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ROLE OF INFLAMMATION IN CARCINOGENESIS*

BY

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The relation of inflammation to cancer is a problem that has interested investigators for many years. Broussais in 1826 seems to have been the first to state that cancer is determined by chronic inflammation. For example, he expressed the view that gastric cancer was preceded by a chronic gastritis. To Broussais chronic irritation was the important factor in the pathogenesis of cancer. With the advent of the cellular theory in pathology, the earlier views of Broussais were either forgotten or neglected. Virchow in the middle of the nineteenth century interpreted the presence of leucocytes around a neoplasm as evidence that a malignant tumour was developing. Virchow (1871) attributed tumour formation to chronic irritation. In modern times these early opinions have been discarded by some, while others have adhered to them.

Ewing (1940) has made an excellent survey of the problem. Various forms of chronic inflammation, according to Ewing, have been observed to precede the appearance of numerous tumours. Precancerous conditions represent in many instances various forms of chronic inflammation. These may be manifested in several different forms such, for instance, as cicatrices from burns or syphilitic lesions. Wolbach (1925) studied the effects of repeated *x*-ray exposures upon the skin antecedent to the formation of carcinoma. He pointed out that the reactions of the epidermis are probably secondary to lesions in the corium. For many years after *x*-ray injury the epidermis proliferates and behaves as in any other reparative process. But, according to Wolbach, continuous proliferative activity in an abnormal supporting tissue predisposes to the development of malignant properties. After viewing many of the forms of precancerous inflammatory conditions, Ewing (1940, 527) arrives, for instance, at these conclusions: "In routine material I find transition stages from hypertrophic endometritis to carcinoma rather frequently, but clinical observations are still inadequate to prove the close dependence of the malignant upon the inflammatory process." In regard to the transformation of benign into malignant tumours, Ewing concludes that some benign growths appear to originate from inflammatory processes and that the involved tissues may present all gradations between single proliferative activity, adenoma, and carcinoma.

Laurens (1941) has pointed out that since carcinogenesis by ultra-violet irradiation is usually preceded by severe erythema, it is possible that the production of neoplasia is related to chronic inflammation. In general, there has been considerable study and evidence on the relation of irradiation to chromosomal aberration and subsequent neoplastic formation. Lacassagne (1933) infected rabbits with a micro-organism, *Streptobacillus caviae*. The infection subsided under the influence of irradiation. Six months to four years later, tumours were found to have developed at the site of irradiation. From these observations Lacassagne concluded that local inflammation seems to be an important factor in carcinogenesis. Burrows and his collaborators (1937) have essentially confirmed these observations. They have induced foci of inflammation in the groin of rabbits by injecting kaolin or silica suspended in olive oil. These areas were subsequently irradiated. Within two years tumours were found to have developed in six out of nine animals.

A number of years ago studies were initiated in my laboratory in an endeavour to throw further light on the role of inflammation in carcinogenesis. I propose to bring to your attention the results of these various studies.

Mechanism of Repair and Formation of Precancerous-like Lesions

The studies of the past twenty-five years have indicated that injured cells in an inflamed area liberate various chemical mediators, which can satisfactorily explain some of the biological manifestations of inflammation (Menkin, 1956a, 1956b). A search was undertaken to determine whether a similar mediator may not likewise be present in exudate which in turn can reasonably explain the mechanism of repair in inflammation. One has to recall that the exudate contains to a large extent the products of cell injury admixed, to be certain, with elements from the circulating blood. The use of blood serum can adequately control for the non-cellular products seeping from the blood-stream. When exudative material obtained from an inflamed pleural cavity of a rabbit is repeatedly injected for months into the tragal part of the ear of rabbits, there developed, several months after cessation of the course of injections, local nodular prominences (Menkin, 1941). Microscopical cross-section through the normal ear reveals a linear-appearing cartilaginous plate and the usual superficial epithelial layer. On the other hand, a section through the area in which repeated injections of exudative materials had been performed reveals a heterogeneous cartilaginous trabecular pattern, or the proliferation of newly formed cartilaginous cells arising from the perichondrial layer (Fig. 1). Occasionally even metaplastic bone transformation may be encountered. The epithelial layer displays considerable degrees of

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hyperplasia with keratin formation, and "tongues" in the epithelial layer dipping down into the corium (Fig. 2) (Menkin, 1941).

When numerous injections of serum, as control, are introduced into the tragal region of the ear, even seven-and-a-half months after cessation of the course of injections, there is no change in the appearance of the cartilaginous plate (Menkin, 1941). When croton oil emulsified in rabbit serum is repeatedly introduced into the tragus of the ear of rabbits for several months, there follows an acute inflammation, which over a period of seven months after the cessation of the course of injections ultimately subsides. Examination of the cartilaginous plate reveals no evidence of any proliferative response. The effect of the injections of exudative material is therefore not directly referable to the inflammation or the repeated injury induced by an irritant *per se*. The observations rather suggest the presence of a growth-promoting component released by injured cells into the exudate. Its presence may give a reasonable explanation for the mechanism of repair after the acute inflammatory process.

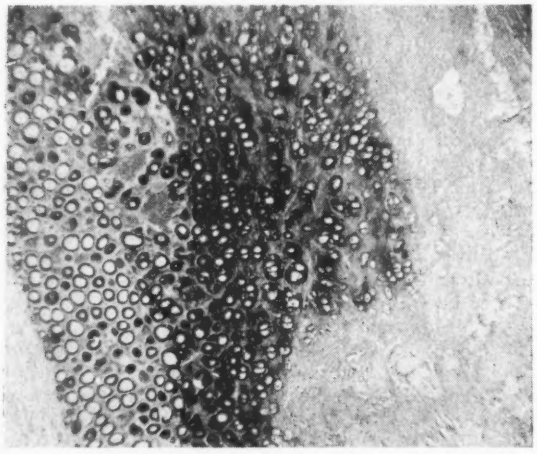

FIG. 1.—Section through the ear of a rabbit. This animal had received 20 injections of exudative material in the ear during a period of about four months. Seven and a half months after cessation of the injections, biopsy revealed marked proliferative activity in the perichondrial region. (×60.) (Taken from Menkin, 1941.)

FIG. 2.—Drawing of microscopical section through the ear of a rabbit at the site of seven successive injections of exudate. Note the hyperplasia of the epithelium dipping downward into the corium and the foci of keratin formation.

An attempt has been undertaken to separate this proliferative factor from the exudate. Fairly satisfactory results have finally been obtained by a very simple procedure (Menkin, 1953, 1956b, 1957). The exudate, usually of canine origin, is dialysed against distilled water for several hours by constantly agitating the "cellophane" tube. The diffusate is then concentrated to about one-tenth its original volume. Intracutaneous injection of this material scarcely induces any inflammatory response, in contradistinction to the toxic euglobulin necrosin, extracted from the indiffusible material remaining in the cellophane tube. Even repeated cutaneous injections of the concentrated diffusate yield a considerably reduced type of effect when compared with that obtained with the necrosin recovered in the indiffusible material. Repeated injections of the concentrated diffusate into the tragus of the ear tends to produce either a mild degree of firmness or else tiny nodular prominences. Microscopical studies may reveal in some parts of the ear newly formed cartilaginous cells growing from the perichondrial layer. On the other hand, a diffusate prepared from canine blood serum, for instance, even after 19 injections during two months, induces no visible change in either the epithelial layer or the cartilaginous plate.

A search has been undertaken for a site that is more responsive to the injections of the diffusate than the tragal region of the ear. Such a region has been found in the breast tissue of non-pregnant rabbits (Menkin, 1953, 1956b, 1957). Repeated injections of concentrated diffusate material in the vicinity of the nipple induce hyperplasia of breast tissue. Even after two weeks, with as few as 11 injections, the hyperplastic involvement of acini and ducts may become quite striking. An untreated nipple in the animal fails to yield any hyperplastic response on the part of the lining epithelium. Concentrated blood-serum diffusate after 12 injections in a period of three weeks into breast tissue of non-pregnant rabbits yields nothing remarkable. On the other hand, 12 injections of concentrated diffusate of exudate in the same period and in the same rabbit induce cystic dilatation of the ducts. When the period of injections is extended, there may be found considerable connective-tissue stroma, and the picture may even be reminiscent of an intracanalicular fibroadenoma. The ducts may at times appear dilated with hyperplasia and even squamous metaplasia of their lining epithelium. The picture recalls that encountered in the chronic cystic mastitis of human beings.

The active principle in the concentrated diffusate has been found to be readily precipitated with acetone (Menkin, 1956b). This precipitate, washed with distilled water and suspended in saline, likewise shows marked hyperplastic responsiveness. Cystic dilatation of the ducts and epithelial "pearl" formation is a frequent

outcome of repeated injections of the acetone-precipitate of the concentrated diffusate (Fig. 3). Dilated ducts may reveal squamous metaplasia and pseudostratification, besides reduplication of the epithelium. As stated above, the picture recalls that of a chronic cystic mastitis. To repeat, neither the diffusate of blood serum nor saline injections reproduce any such effects; and the resulting picture is not appreciably greater than that of an untreated nipple in the same rabbit.

The growth factor of exudates affects likewise the cutaneous epithelium and hair follicles in the vicinity of the injected nipples. Nature's contribution of several nipples renders this a propitious animal. One of the nipples, for instance, can be utilized as an untreated control. The hair follicles in its vicinity show nothing remarkable. After numerous injections of the concentrated diffusate—for example, 85 injections—for six months—marked hyperplasia of the cutaneous follicular epithelium is seen. The acetone-diffusate precipitate likewise causes a marked hyperplastic response (Fig. 4). As control, the repeated injections of saline induce no effect on the follicular epithelium.

A study was undertaken to determine whether the combination of the growth factor of exudate and a carcinogenic hydrocarbon would induce a synergistic or enhanced effect (Menkin, 1959). Rous and Friedewald (1944) reported that the application of methylcholanthrene and tar to virus-induced papillomas of the domestic rabbit hastens the formation of carcinomatous structures, and that the malignant changes are often multiple. Rogers and Rous (1951) also showed that scarified areas of rabbit skin previously rendered hyperplastic with turpentine and then inoculated with Shope papilloma virus develop carcinomatous changes in many cases, after several months, provided that the areas were also covered with a dressing that contained 20-methylcholanthrene or 9:10-dimethyl-1:2-benzanthracene. According to these investigators the virus and the hydrocarbon seemed to act jointly in their carcinogenic capacities.

Deelman (1924) had reported that wounds in a tarred region hasten and localize the formation of tumours. Orr (1935) reported that fibrosis of the subcutaneous tissue caused by the insertion and subsequent removal of linen threads induces accelerated tumour in mice by means of 1:2:5:6-dibenzanthracene. Cramer (1929) found that injury by cautery to a tar-wart papilloma tends to favour the development of malignancy. According to Berenblum (1941, 1944), once a preneoplastic state has been induced by a true carcinogen a

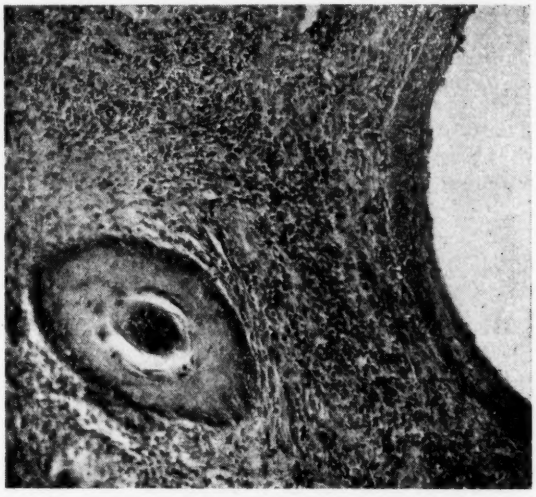

FIG. 3.—Twenty injections of the acetone precipitate of the diffusate of an exudate for about one month. Note the epithelial "pearl" formation and the epithelial hyperplasia around part of a widely dilated duct. The epithelial layer in the duct displays a pattern of pseudostratification with squamous metaplasia. The picture is somewhat reminiscent of the chronic cystic mastitis seen in human beings. (×111.) (Taken from Menkin, 1956b.)

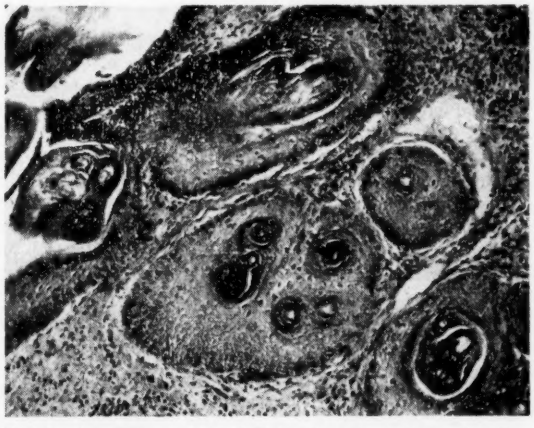

FIG. 4.—Appearance of hair follicles six and a half months after 85 injections in the nipple of the acetone precipitate of the diffusate of exudates suspended in saline. The hyperplasia and keratosis are striking but there are no signs of any invasiveness. (×108.)

TABLE I.—*The Effect of the Growth-promoting Factor of Exudates with or without Superimposed Paintings with Methylcholanthrene on the Breast Tissue of Rabbits*

Rabbit No.	No. of Injections of Growth-promoting Factor and Number of Paintings with Carcinogenic Hydrocarbon	Duration of Experiment (Months)	Volume of Breast Tissue Underlying Nipple (c.cm.)				
			Untreated Nipple	Nipple Painted with Methylcholanthrene	Nipple Injected with Concentrated Diffusate	Nipple Injected with Concentrated Diffusate Plus Painting with Methylcholanthrene	Nipple with Methylcholanthrene Plus Saline Injections
28–89	54	4·5	0·36	1·42	0·83 4·88	6·3 17·21	
38–93	60	6	0·75	0·64	1·41 1·57	9·61	
28–97	127	11·5	0·22	0·49	1·14	4·13 5·14	0·56
28–58	127	11·5	0·45	0·27	2·08	11·07 6·18	1·09
Average	92	8·4	0·45	0·71	1·99	8·52	0·83

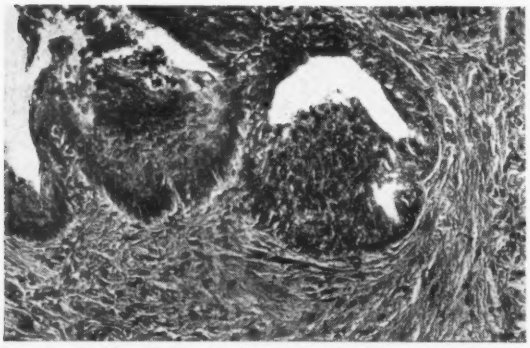

FIG. 5.—*Rabbit 29–27.* 88 injections of concentrated diffusate in the vicinity of a nipple followed by 88 paintings of 1% methylcholanthrene in acetone for eight months has induced marked proliferative introductal activity of the lining epithelium with squamous metaplasia. (×139.)

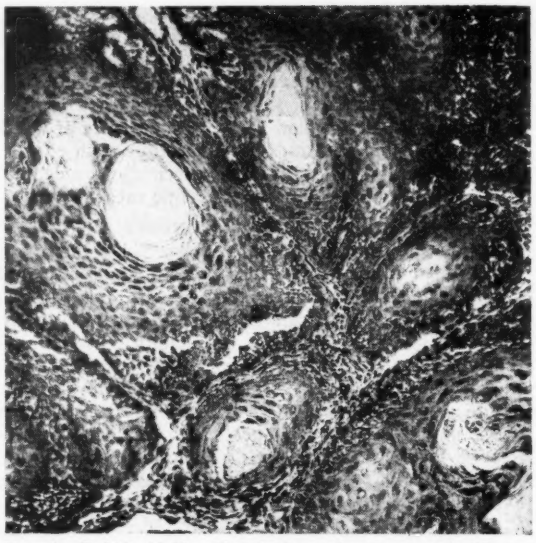

FIG. 6.—*Rabbit 44–22.* 52 injections of concentrated diffusate of exudate in the nipple region followed by 52 paintings of 1% methylcholanthrene in acetone over a period of four and three-quarter months has induced in the treated cutaneous area a squamous carcinoma. (×123.)

benign tumour can be made to appear at that site. Subsequent progress to a carcinoma can then be hastened by a variety of non-carcinogenic irritants. Boutwell, Bosch, and Rusch (1957) have demonstrated that small amounts of croton oil applied to susceptible mice induce papillomas and, subsequently, carcinomas in a certain percentage of treated animals. The response to croton oil is greater when the mice have previously been treated with a subcarcinogenic dose of 9:10-dimethyl-1:2-benzanthracene.

The observations on the combination of the growth factor and methylcholanthrene indicate a synergistic effect. In Table I are assembled some typical results of several experiments. The volume of breast tissue underlying each nipple is obtained by measuring length, breadth, and thickness with a calliper. Typical measurements collected in Table I indicate that the growth factor induces an average increase in volume amounting to almost five times that of the untreated nipples; whereas the combination of the growth factor and a carcinogenic hydrocarbon results in an average increase in volume of almost 20 times that of the controls (Table I).

Methylcholanthrene paintings alone fail to induce any significant increase in volume of breast tissue. After 88 paintings of 1% methylcholanthrene in acetone for a period of eight months, one encounters no appreciable change on the part of the lining epithelium in ducts and acini; while the repeated injections of the growth factor followed by paintings with the carcinogenic hydrocarbon for a similar period induce marked epithelial growth into the lumina of some of the ducts and acini (Fig. 5). Prolonged administration, such as 54 injections of the diffusible growth factor followed by paintings with methylcholanthrene for six months, induce in rabbits the formation of papillomas. This is not encountered when there are only repeated injections of the concentrated diffusate, and infrequently by merely repeated paintings. It therefore appears as if the growth factor of exudates behaves as a cocarcinogen-like substance to a carcinogenic hydrocarbon—that is, methylcholanthrene. When the concentrated diffusate of blood serum is substituted for that of exudate, no such accelerated development of papillomas tends to occur in a similar interval.

In conclusion, it appears as if the role of inflammation in carcinogenesis is that of a cocarcinogen via the growth factor of exudates. It is difficult to induce a cancer in rabbits with a carcinogenic hydrocarbon. The combination of the growth factor of exudates and methylcholanthrene has in very few cases induced a

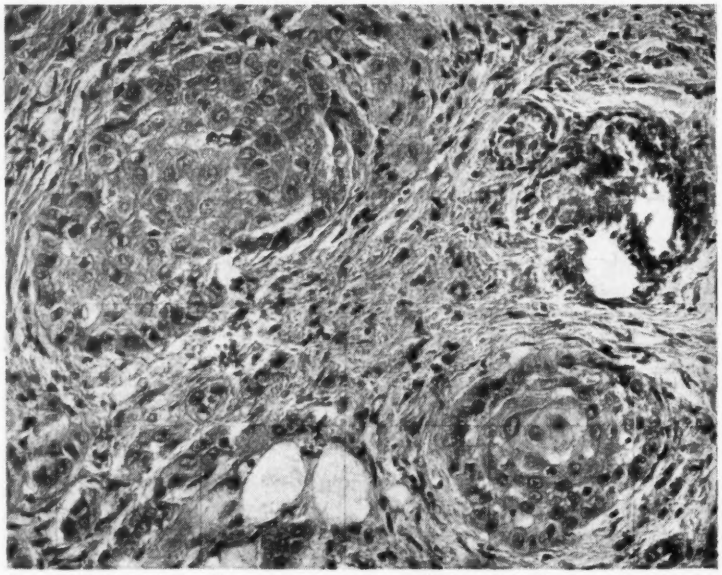

FIG. 7.—*Rabbit 44–22.* The squamous carcinoma illustrated in Fig. 6 has invaded the corium. Note "pearl" formation in one of the carcinomatous islets. (×200.)

squamous carcinoma. This is illustrated in Fig. 6. This effect has been obtained after 52 injections of the growth factor and 52 local paintings of the carcinogenic hydrocarbon for a period of four and three-quarter months. Painting alone for the same interval has merely induced hyperkeratosis of the hair follicles and hyperplasia of the epithelium. The squamous carcinoma induced by the combination of the growth factor and the hydrocarbon invades the deeper layer of the corium (Fig. 7). In brief, it is conceivable that the studies of numerous investigators, some of whom have been cited above, on the mechanism of cocarcinogenicity by various irritants—for example, croton oil—may be referable to the induction of an inflammation. Following the eventual mild degree of cellular injury, and the consequent release of the growth-promoting factor, there may be a hastening in development of a neoplasm in the presence of a carcinogen.

Irreversible Effect Induced by the Growth-promoting Factor of Exudates

When the growth factor is injected for a relatively brief period, the enlarged nipple tends to regress. When, however, the course of injections is maintained for several months and is at least above 30, there is a tendency for a state of irreversibility to be established even though administration of the active growth material is discontinued. This is illustrated in Figs. 8 and 9. In this experiment the breast was injected 61 times for a period of five and a half months. The injections were then discontinued. Three months later not only had the volume of the breasts not regressed, but, if anything, they had enlarged further. Nevertheless, the growth factor *per se* can only favour, after multiple injections, the establishment of a relative irreversible state; yet by itself it fails to induce a neoplasm. Rather, as mentioned already, it behaves as a cocarcinogen, thus pointing to a definite role of inflammation in carcinogenesis via the growth-promoting factor of exudates.

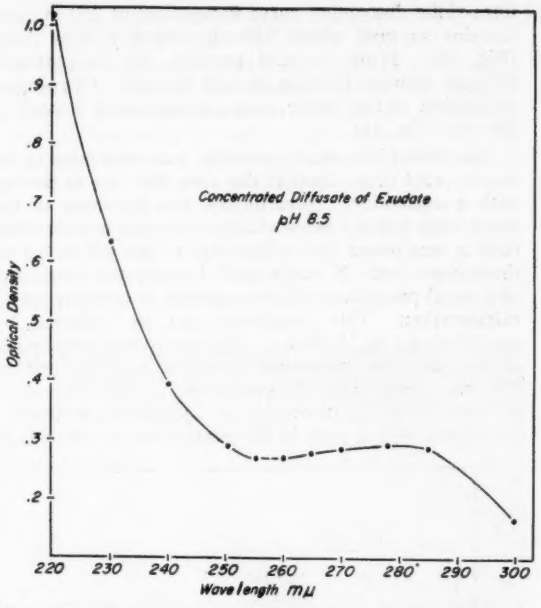

FIG. 10.—The concentrated diffusate of an alkaline exudate is at an alkaline *p*H. The ultra-violet absorption curve levels off at 250 mμ. and this is maintained until about 285 mμ.

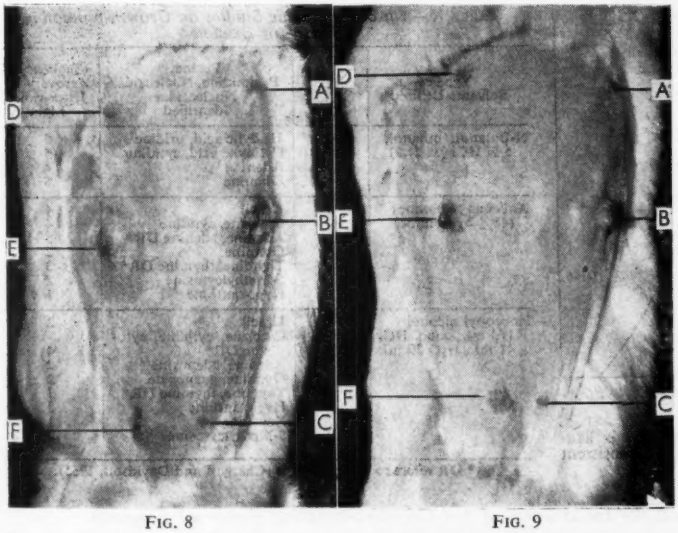

FIG. 8 FIG. 9

FIG. 8.—*Rabbit 27-07.* For almost five months the nipples of this non-pregnant rabbit were treated as follows. A: untreated. B: 61 injections of the concentrated diffusate of an exudate. C: 61 injections of physiological saline. D: 61 paintings with 1% methylcholanthrene in acetone (the first 22 paintings consisted of methylcholanthrene in olive oil, 5% and 1%). E and F: 61 injections of the concentrated diffusate of an exudate plus 61 paintings with 1% methylcholanthrene in acetone (the first 22 paintings consisted of methylcholanthrene in olive oil 5% and 1%). At this stage the B and E nipples show definite enlargement. The administration of the concentrated diffusate or the paintings, or of both, were discontinued, and the nipples were subsequently studied for any irreversible effects (see Fig. 9). FIG. 9.—*Rabbit 27-07.* About three months after cessation of injections of the concentrated diffusate of exudate in the B area the enlargement of the nipple has not regressed. In fact, it appears to be somewhat more prominent than at the termination of the course of injections (see Fig. 8). Note, therefore, the irreversible effects induced by the repeated injections of the proliferative factor of exudates. A similar irreversibility of effect seems to have occurred in the E nipple, in which repeated concentrated diffusate injections and paintings had been administered prior to cessation three months before.

On the Nature of the Growth-promoting Factor of Exudates

Studies have been undertaken in an endeavour to determine the nature of the growth factor in exudates. Chromatographic studies by my former associate, Dr. Kalnins, on the hydrolysate of the exudate indicated the presence of a peptide (Menkin, 1957). The amino-acids identified were leucine, valine, lysine, α-alanine, glycine, aspartic acid, and serine (Menkin, 1957). Glutathione seemed also to be present.

Further studies were carried out with a DU spectrophotometer on the concentrated diffusate of exudate. As the inflammatory reaction progresses, the exudate is at first at an alkaline *p*H level, eventually assuming an acid level (Menkin, 1934, 1940; Menkin and Warner, 1937). The *p*H of the concentrated diffusate parallels the changes in the hydrogen-ion concentration of the exudate. With the latter at an alkaline *p*H the concentrated diffusate is at about *p*H 8 or 8.5. The

ultra-violet absorption curve flattens out at 250 mμ and remains so until about 285 mμ, when it dips down (Fig. 10). From an acid exudate, the concentrated diffusate assumes likewise an acid reaction. Ultra-violet absorption shows under such circumstances a peak at 260 mμ (Fig. 11).

The diffusibility, thermostability, and absorption in the nucleic acid range support the view that one is dealing with a nucleotide. Nevertheless, the flattening of the curve after 250 mμ in an alkaline diffusate was puzzling until it was found that adjustment of the *p*H to 4.5 or thereabouts with N acetic acid favours the formation of a small precipitate which augments in quantity under refrigeration. This precipitate can be collected by centrifuging it at 21,600 × *g*. The ultra-violet absorption of the aqueous suspension yields a peak at 260 to 270 mμ (Fig. 12). Evaporation to dryness of a diffusate yields on suspension in an aqueous medium a precipitate with a peak in the peptide range. This fact,

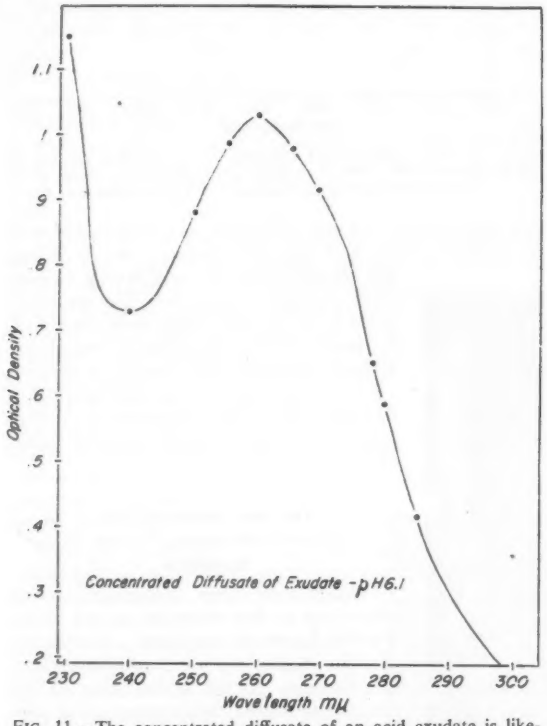

FIG. 11.—The concentrated diffusate of an acid exudate is likewise acid. There is a peak of absorption at 260 mμ consistent with a nucleotide.

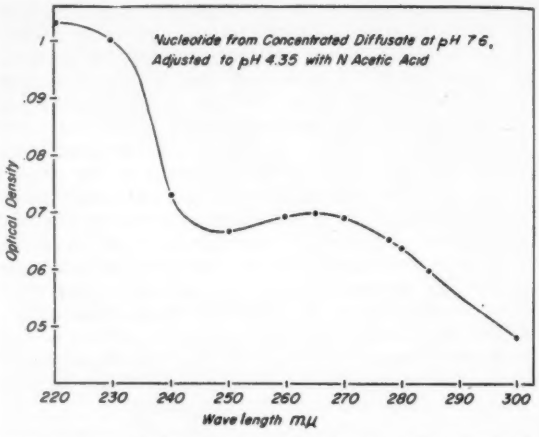

FIG. 12.—An alkaline diffusate derived from an alkaline exudate when adjusted with N acetic acid to *p*H 4–4.5, or thereabouts, forms a small precipitate. This precipitate suspended in an aqueous medium yields a peak of absorption at 265 mμ, consistent with nucleotides.

in addition to the chromatographic studies by Kalnins on the acid hydrolysate of the active diffusate, as well as the inability of nucleotides to be precipitated at *p*H 4.5 by acetic acid, supports the view that the factor may well be a *nucleopeptide*. Descending chromatographic studies with three different solvents support the presence of a nucleotide or related groups in the growth factor (Table II). Finally, recent observations indicate that

TABLE II.—*Chromatographic Studies on Growth-promoting Factor of Exudates*

Type of Solvents Utilized	No. of Observations	Purine, Pyrimidine, Nucleoside, Nucleotides Identified	Frequency of Recovery by Ultra-violet Light
N-Butanol, ethanol, 5 N HCl (3 : 2 : 2)	6	Uridylic acid, uridine	6
		Cytidylic acid, cytidine	5
		Adenine	4
		Guanine	6
Aqueous N-butanol (86% by volume)	5	Uracil	4
		Cytosine, cytidine	4
		Adenine, adenine DR*	5
		Guanine	2
		Thymine, thymine DR*	3
		5-Methylcytosine	2
		Hypoxanthine	1
Isopropyl alcohol 170 ml., conc. HCl 41 ml., H_2O 39 ml.	4	Uracil	2
		Cytosine, cytidine, cytosine DR*	4
		Adenine, adenosine	2
		Guanine, guanosine	2
		Thymine, thymine DR*	3
		Hypoxanthine	3
		Xanthine	1
		5-Methylcytosine	2

* DR refers to deoxyriboside (Chargaff and Davidson, 1955).

TABLE III.—*Effect of Ribonuclease on the Inactivation of the Growth-promoting Factor of Exudates*

Rabbit No.	No. of Injections of Growth-promoting Factor With and Without Exposure to Ribonuclease	Duration of Experiments (Months)	Volume of Breast Tissue Underlying Nipple (c.cm.)			
			Untreated Nipple	Nipple Injected with Concentrated Diffusate	Nipple Injected with Concentrated Diffusate but Hydrolysed Previously with Ribonuclease	Nipple Injected with Distilled Water
5291	24	2	0·99	1·45 3·46	1·14 0·89	0·87
5292	28	2·5	0·58	2·24 3·02	0·16 1·90	0·39
5293	25	2·5	0·23	0·55 1·71	0·12 0·10	0·23
3303	15	1	0·91	1·53 0·96	0·48 0·81	—
Average	23	2	0·68	1·87	0·70	0·50

when the concentrated diffusate of exudates containing the growth factor is treated with trypsin or with ribonuclease, the active principle in the growth factor is inactivated (Figs. 13 and 14). The data in Table III indicate that ribonuclease inactivates the factor. This type of evidence with appropriate enzymes would perhaps support the characterization of the growth factor of exudates as a *nucleopeptide*. Further chemical studies, however, are in progress to substantiate this view.

This nucleopeptide is biologically active in inducing an enlargement of breast tissue. For instance, seven weeks after the cessation of a course of 34 injections of the nucleopeptide, the enlarged breasts are found conspicuously enlarged. Three and a half months after the termination of the course of injections, the breasts have not regressed in size (Fig. 15). Even six months afterwards the irreversible state of enlargement is to a great extent still present. The microscopical picture of the breast tissue seven weeks after 22 injections of the nucleopeptide displays a picture not unlike that seen in chronic cystic mastitis. There is marked proliferative activity of the epithelium into the lumen of the ducts (Fig. 16). Contrast this with the ducts in an untreated nipple in the same animal (Fig. 17). The cutaneous epithelium in the vicinity of the nipple is likewise hyperplastic after injections of the nucleopeptide. The hyperplasia is marked around the hair follicles. Follicular keratosis forms also a conspicuous feature.

In conclusion, the mechanism of repair in inflammation seems to be referable to liberation by injured cells of a diffusible growth factor, possibly a nucleopeptide, which can be recovered in exudates. Its repeated injections may induce a relatively irreversible state. In the breast tissue the resulting picture resembles that of a chronic cystic mastitis. The surrounding cutaneous and follicular epithelium becomes very hyperplastic after repeated injections of this active growth factor. Finally, in conjunction with a carcinogenic hydrocarbon the growth factor behaves as a carcinogen. The presence of such a tool liberated by injured cells defines the role of inflammation in carcinogenesis. It would appear as if inflammation through the growth factor acts as a cocarcinogen to an exogenous carcinogen, and even possibly to an endogenous carcinogen liberated as a result of genetic predilection. In other words, inflammation hastens and perhaps intensifies the neoplastic process, in turn initiated as a consequence of a genetic susceptibility or mutation.

Carcinogenesis and Cellular Injury

If I may express my own view, it seems conceivable that derangement in the biology of the cell leading eventually to neoplastic formation may be referable to a disequilibration of the cell brought about by a variety of means. This may be in the form of a long-standing inflammatory process or chronic irritation, virus infection, or hormonic imbalance. The result of such disequilibration may be a relatively low-grade injury to the cell which in turn releases the growth-promoting or proliferative factor described in this discussion (Menkin, 1956b). This factor *per se* is apparently

FIG. 13.—*Rabbit 52-94.* Breast tissue after seven injections of concentrated diffusate of exudate within a period of three weeks. Note the distended and cystic appearance of the ducts. On the upper right-hand corner some of the hyperplastic cutaneous epithelium is in evidence. (×100.)

FIG. 14.—*Rabbit 52-94C.* Breast tissue after seven injections of concentrated diffusate of exudate within a period of three weeks. The concentrated diffusate was previously hydrolysed with ribonuclease. Note in contrast to the illustration in Fig. 13 that there is no distension of the breast tissue, nor any cutaneous epithelial hyperplasia (lower left-hand corner). This observation on the inactivation of the growth factor with ribonuclease would indicate that activity is closely associated with the nucleotide part of the molecule in the growth-promoting factor. (×100.)

insufficient to develop a true tumour, but, as emphasized already, in a genetically susceptible organism or in the presence of a carcinogen it may favour neoplastic development (Menkin, 1956b).

To us, inflammation and neoplastic formation are both manifestations of cellular injury. Inflammation can be regarded as a manifestation of severe cellular injury in vertebrates, whereas neoplastic growth may be the expression of relatively mild protracted cellular injury with the consequent release of the growth-promoting factor, but in a genetically susceptible organism.

Hypotheses are useful only if they can furnish soil for further experimentation and therefore lead to scientific progress. With this point of view that the degree of injury may perhaps be a significant factor to consider, the following simple experiments were conducted.

About 70 rabbits received a mild type of long-standing injury by merely piercing the ear lobe with staples and fixing a metal tag held on the external surface of the ear (Menkin, 1955, 1956b). The extruding staples were bent and twisted on the inner surface of the ear. The tags were thus maintained for several months, and in

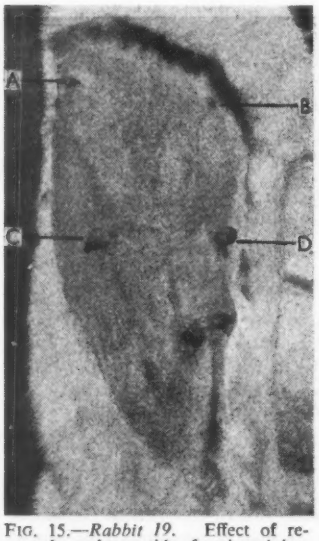

FIG. 15.—*Rabbit 19.* Effect of repeated nucleopeptide fraction injections on the breast tissue of a non-pregnant rabbit. Upper nipples A and B are untreated. Lower nipples C and D have been injected 34 times each with the nucleopeptide suspension of exudates over a period of three months. Photograph taken 3½ months after cessation of injections. Note that the nipples are markedly enlarged and have not regressed even though the course of injections has been discontinued for 3½ months.

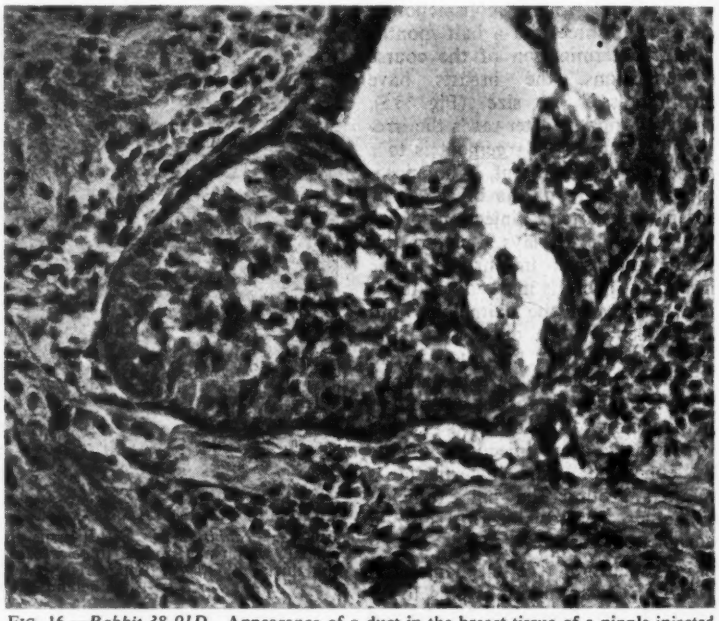

FIG. 16.—*Rabbit 38–91D.* Appearance of a duct in the breast tissue of a nipple injected 22 times with the nucleopeptide of exudates over a period of seven weeks. Note marked hyperplastic effect of the epithelium as it protrudes into the lumen. The appearance recalls that encountered in the chronic cystic mastitis of human beings. (×224.)

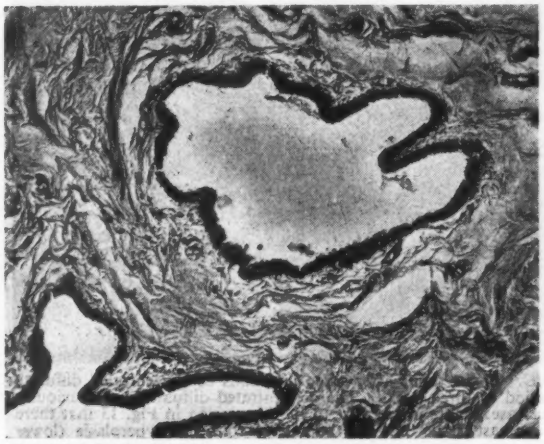

FIG. 17.—*Rabbit 38–91A.* Appearance of ducts in an untreated breast tissue taken from same animal as illustrated in Fig. 16. The epithelial lining of the ducts is normal, in contrast to the experimental appearance shown in Fig. 16. (×120.)

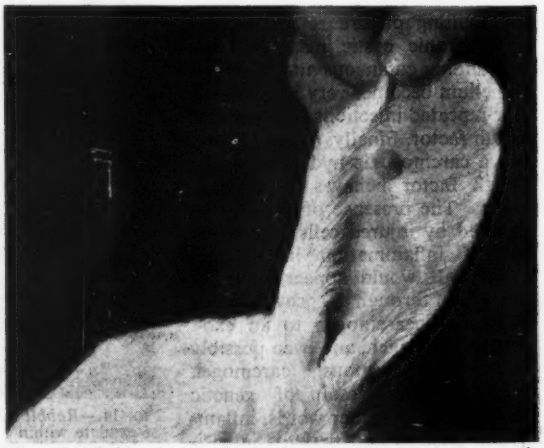

FIG. 18.—*Rabbit 63–36.* Small circumscribed neoplastic growth in area of ear pierced about four months previously with staples to hold throughout that period the ear tag on the outer ear. Note that with mild degree of sustained injury new growths develop in about 25% of the rabbits studied. (Taken from Menkin, 1956b.)

FIG. 19.—*Rabbit 63-36.* Microscopical section of tumour shown in the gross in Fig. 18. The presence of islets of cartilage cells in a disorganized fibromatous stroma would suggest a chondrofibroma. The tumour has developed within a period of four months. (×22.) (Taken from Menkin, 1956b.)

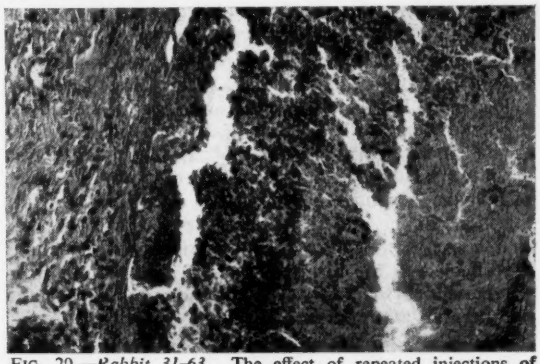

FIG. 20.—*Rabbit 31-63.* The effect of repeated injections of necrosin, the toxic euglobulin of exudates, on the breast tissue. Within a period of six weeks 17 injections of that substance were introduced into or in the vicinity of a nipple. Note the acute necrotizing reaction, with disappearance to a large extent of the normal architecture of the breast tissue. (×142.) (Taken from Menkin, 1956b.)

two cases for over two years. About one-quarter of the rabbits developed small nodules at the site where the staples were extruding on the inner surface of the ear lobe (Fig. 18). Microscopical studies of these nodules revealed cartilaginous islets in a disorganized connective-tissue stroma (Fig. 19). The lesion is a benign tumour which may be termed a chondrofibroma. Biopsy is followed by secondary growth at the site of the excised tumour. An appropriate question that may be raised is why only 25% of the cases have developed tumours. There may be several interpretations on this point. To us it seems conceivable that only 25% of the rabbits carried genetic predilection to tumour formation. With the concomitant release of the growth-promoting factor from the site of mild injury over a prolonged interval, it is quite conceivable that the development of a local neoplasm occurs only in susceptible rabbits. This is one interpretation, but it is readily admitted that perhaps other explanations may be advanced.

Another experimental observation may be pointed out in regard to the view that the degree of cellular injury may be significant enough for consideration. The injury factor which determines the pattern of injury in inflammation is a euglobulin termed necrosin (Menkin, 1943). Repeated injection of necrosin into the nipple region of a non-pregnant rabbit is followed by a marked necrotizing inflammation. The architecture of the original tissue at the core of the abscess is completely obliterated (Fig. 20). On the other hand, at the periphery of the site of necrosin injections, where the concentration of necrosin is diminished and therefore the degree of injury is reduced, not only are dilated cystic ducts seen, but their epithelial lining may display evidence of proliferation, squamous metaplasia, pseudostratification (Fig. 21).

I believe that at this point I should stop, for our understanding of the complex mechanism at play has reached its limit for the present. For instance, we are wholly at a loss regarding the exact nature of the determinants concerned in the degree of induced cellular injury. Is it referable to an enzymatic disturbance or to the concentration of the irritant? Does the quantitative liberation of necrosin by an injured cell enter into play? These are all problems for the future to uncover. I only hope that curiosity has been aroused in an endeavour to understand further the significance and the mechanism of action of the endogenous growth-promoting factor liberated by injured cells.

Summary

The history of this subject, dating from the early studies of Broussais in France and Virchow in Germany

FIG. 21.—*Rabbit 31-63.* After 17 injections of necrosin, the injury factor of exudates, in the nipple region there follows within six weeks, as seen in Fig. 20, complete destruction of the core of the involved tissue. However, at the periphery of such areas, where the necrotizing effect is not quite so acute, one may encounter epithelial hyperplasia of ducts with pseudostratification. The picture is not wholly dissimilar to that met with in chronic cystic mastitis. (×154.) (Taken from Menkin, 1956b.)

to the more recent studies of Ewing, Lacassagne, and Burrows, is briefly described. In recent years I have demonstrated the presence of a growth-promoting factor in inflammatory exudates. This factor offers a reasonable explanation for the mechanism of repair. Its growth properties can be elicited by repeated injections in either the ear or the breast tissue of rabbits. In the latter area a picture resembling that seen in chronic cystic mastitis of humans is frequently obtained as a result of repeated injections of the growth factor in non-pregnant rabbits. In the ear, both epithelial and cartilaginous structures are affected in the form of marked proliferation from the perichondrium as well as pronounced hyperplasia and keratinization on the part of the epithelium.

The growth-promoting factor of exudates is diffusible, and as such it can be obtained by dialysis and subsequent concentration of the diffusate. It is heat-stable. Repeated injections tend to produce a state of irreversibility, so that the enlarged breast fails to regress upon cessation of the course of administration. Nevertheless, the factor *per se* fails to induce an autonomous neoplastic process. It has, however, been demonstrated that the growth factor of exudates behaves as a cocarcinogen when combined with a carcinogenic hydrocarbon—for example, methylcholanthrene. This appears to be the role of inflammation in carcinogenesis—namely, that of a cocarcinogen via the growth-promoting factor, liberated in turn by injured cells at the site of inflammation.

Absorption as well as chromatographic studies support the view that the growth-promoting factor of exudates contains peptide and nucleotide structures involved in its activity. The possibility that the factor is a nucleopeptide is envisaged, and is therefore being considered. Inactivation of the factor by both trypsin and ribonuclease supports such a view.

The problem of carcinogenesis and cellular injury is discussed. It is pointed out that severe cellular injury leads to the development of inflammation, while mild injury tends to produce proliferative activity. Basically, neoplastic formation appears to depend on genetic susceptibility, which, in turn, can be intensified, accelerated, or reinforced by the liberation of the endogenous growth-promoting factor of exudates, acting thus as a cocarcinogen.

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RHEUMATOID NEUROPATHY*

BY

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AND

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"Nobody is on my side, nobody takes part with me: I am cruelly used, nobody feels for my poor nerves."
—Mrs. Bennett in *Pride and Prejudice*.

A sufferer from rheumatoid arthritis has enough to contend with in attempting to live in rough harmony with his painful, stiff, weak, and swollen joints. The addition of peripheral neurological features may make life even more unbearable for him and may necessitate admission to hospital and a greater degree of disability and crippling in the future. This complication of rheumatoid disease, for so we consider it, was forcibly brought to our notice three years ago, when four out of eight in-patients presented with sensory signs in the legs; one had motor weakness also, being unable to dorsiflex one foot. The fact that half our in-patients with rheumatoid disease at that time had peripheral neuritis was a pure coincidence, for the complication is relatively uncommon, but it started us on our present investigation (Hart *et al.*, 1957).

We have now seen a total of 25 such cases in our own unit and a further 17 in the clinics of colleagues who have kindly allowed us to see their patients and their records. An increasing number of cases have been reported in the last three years in the world's literature, mostly from the United States of America, where steroid therapy has largely been blamed for its emergence as a clinical entity. In this country, however, we have seen several cases which have never received steroids, and a neuropathy in rheumatoid disease was reported as long ago as 1887 by Pitres and Vaillard, in France, and in this country in 1898 by Bannatyne, who, in a book on rheumatoid arthritis, recognized it as a systemic disease and stated, "in a certain number of cases peripheral neuritis has been noticed, but in so far as to negative any idea that this [neuritis] is the cause of the [rheumatoid] disease"; and again, "in the cases where the reflexes are absent it is almost certain that we have to do with a neuritis probably set up by the joint inflammation or by toxins." The late W. H. Allchin (1900) wrote: "Definite peripheral neuritis has been demonstrated in a few cases [of rheumatoid arthritis] though not in the nerves which actually supply the joints."

In the last 30 years increasing emphasis has been placed on the systemic manifestations of rheumatoid arthritis (Fingerman and Andrus, 1943; Bauer and Clark, 1948; Calkins and Bauer, 1955), and a pathological study by Sinclair and Cruickshank (1956) has emphasized the widespread nature of rheumatoid

*Based on a paper read at the 4th European Rheumatological Congress in Istanbul, September, 1959.

arthritis. Various reports appeared concerning the histology of nerves and muscles in rheumatoid arthritis, focal collections of round cells occurring commonly (Freund *et al.*, 1942; Gibson *et al.*, 1945; Morrison *et al.*, 1947), but until recently there was relatively little in the literature regarding neuropathic changes in rheumatoid arthritis, though it was known to occur relatively often in polyarteritis nodosa. Its occurrence in systemic lupus erythematosus is also well recognized (Heptinstall and Sowry, 1952).

As the systemic features of rheumatoid arthritis have been more widely appreciated, so it has become apparent that these three so-called "collagen" disorders have no fixed, firm barriers; changes in serum proteins, positive sheep-cell agglutination tests, or development of L.E. cells in the circulating blood may occur in all on occasion. There seems to be, in fact, a merging pattern of these disorders, and we have come to recognize a clinical picture of "complicated rheumatoid arthritis" short of the full development of polyarteritis nodosa or systemic lupus erythematosus. It is in this complicated group that peripheral neuropathy occurs more commonly. The usual case is of long-standing rheumatoid disease with subcutaneous nodules, high-titre positive differential agglutination test (Rose–Waaler test), features of therapeutic hypercortisonism, marked changes in the serum electrophoretic pattern, and polyarteritic and neuropathic features. Though milder and less serious cases occur we consider that the development of this full clinical picture is of grave prognostic importance. Mason and Steinberg (1958) are of the same opinion. Epstein and Engleman (1959) go further and state that steroids should not be used in this group of patients.

Clinical Study

We now have details of 42 cases, 25 from our own unit. Of these 42 patients, 18 were men and 24 were women, their ages ranging from 36 to 88 years, the large majority being between 40 and 60. 15 had had no steroids within a period of three years from the onset of neuropathy, and 12 had never had steroid therapy at any time prior to the development of the neuropathy. 20 were on a regular dose of steroid and had no history of recent alteration in dosage; in six reduction or withdrawal of steroid therapy had apparently precipitated neuropathic changes. Except in a few cases, steroid therapy had been given continuously for one to five years before the onset of neuropathic changes. Visible arteriopathic changes were present in 6 of the 42 at the time of onset of the neuropathy, in two cases coming on at the same time. Phenylbutazone and gold appeared to play no part in precipitating symptoms in any case. Rheumatoid nodules were present in 24 cases and absent in 15; in 3 the records are inadequate. The D.A.T., or Rose–Waaler test, was not done or recorded in eight cases, but in the other 34 it was negative in 5 and positive in 29, usually in high titres. In almost all cases where neuropathy occurred on regular dosage prednisone or prednisolone was being given at the time of onset, but one case occurred on corticotrophin therapy.

The newer steroids, triamcinolone, methylprednisolone, and dexamethasone, have not yet been used extensively long enough for anything to be said about the relative incidence of neuropathy with the different steroids; it is of interest, however, that a change to a new steroid in comparable dosage appeared to trigger off the neuropathy in three cases—two on changing from cortisone to prednisolone, one from prednisolone to dexamethasone—and in two further cases manipulation of dosage of different steroids in the preceding few weeks may have played a part. Motor weakness occurred in 18 cases, always when sensory changes were considerable. Marked weakness or absence of dorsiflexion of the foot was the best guide. This was positive in both legs in seven cases, in one leg in seven, and in all four limbs in four, marked weakness in finger movement and grip also occurring. This assessment of muscle weakness had to be carefully done, as rheumatoid changes in joints cause pain and weakness, and this had to be carefully considered in every case. The important point in differentiation lay in the temporal relationship between fresh muscle-weakness and the onset of neuropathic change.

In all cases where muscle power was affected, sensory changes were relatively advanced. In two cases transient unilateral facial hypoaesthesia was noted at the time of development of the neuropathy, but its significance is uncertain. Ankle reflexes were much reduced or absent bilaterally in eight cases, unilaterally in four. The pattern of the neuropathy was symmetrical in 26, asymmetrical in 16. L.E. cells were found in only four patients, but in no case could the diagnosis of systemic lupus erythematosus be seriously considered. In four cases a skin condition variously named livedo reticularis or livedo racemosa, said to be a skin manifestation of polyarteritis nodosa (Ketron and Bernstein, 1939; Talbott and Moleres Ferrandis, 1956), developed during the course of rheumatoid neuropathy.

It may be of significance that arteritis and neuropathy have not to date, to our knowledge, been reported in other conditions treated by steroids, such as asthma or ulcerative colitis, but only in the collagen disorders. This may, however, be due to the fact that few other disorders are treated for such long periods continuously.

Mode of Onset

In 13 cases the neuropathy appeared abruptly and painfully, so that the patient could state the day and even the approximate time when symptoms were first noticed; in the remaining 29 cases the onset was more gradual and insidious. In only 3 of these 29 cases was the appearance of the neuropathy at a time of overall exacerbation of the rheumatoid disease. Though in six cases the appearance of neuropathic features was related to reduction or cessation of steroid dosage, one, when started on prednisolone, cleared in a month and one improved when started on corticotrophin. In two cases steroid therapy was abruptly stopped by the patients after the development of the neuropathy, without any alteration in the signs and symptoms.

Progress

The course of the neuropathy has often been difficult to assess. Some cases have remained constant and unchanged over periods of observation up to four years; others have improved, with some residual neurological change; some have fluctuated, improving and worsening at different times; some have disappeared completely. At the time of this review or at death 20 cases appeared relatively constant and unchanged; 14 have improved, sometimes after marked fluctuation in the past; two steadily deteriorated before death; five have apparently recovered completely; and one continues to fluctuate erratically. Of the 15 patients not given steroid therapy

for the previous three years, two have worsened, one has fluctuated erratically, six have remained constant, five have improved, and one has completely recovered within one month of starting prednisolone by mouth. Two patients who developed neuropathy before receiving steroids and who were later started on prednisolone suffered an exacerbation of symptoms and a severe worsening of their neuropathy, one on withdrawal and one on constant dosage. Of the seven fatal cases, four had been on prolonged steroid therapy, two had suffered an exacerbation of symptoms on sudden withdrawal of steroids, and one had not received this therapy. In these fatal cases the neuropathic features worsened prior to death in two cases, improved in one, and remained relatively unchanged in four.

As regards treatment, nothing given has conclusively improved the neuropathy. Occasional fluctuations make assessment difficult, but neither moderate increase in steroid dosage nor vitamin administration or anything else we have tried has appeared to make any real difference. Estimations of the plasma vitamin B_{12} in the last nine cases have all been entirely normal.

Clinical Picture

The more usual mode of onset was of numbness or "deadness" in toes and feet, or of an intolerable burning pain. The complaint was usually bilateral or symmetrical, though one leg was commonly more extensively involved than the other. The pressure of bedclothes, even socks, was often intolerable to the sufferer. It was in general only in the more severe cases, where sensory changes were marked and extensive in the feet, that fingers and hands were also involved. Excessive sweating was noted in only one case—a male patient under the care of Dr. R. R. Bomford at the London Hospital. In this patient so severe was the hyperaesthesia over the soles of the feet that walking was prevented by this alone. Weakness of foot movements, notably dorsiflexion, or of grip was complained of in the more severe cases with extensive sensory changes in the legs. On examination all modalities were found to be reduced in the affected areas; light touch, pin-prick, two-point discrimination, heat and cold, and vibration sense were usually markedly affected, but position sense usually remained well preserved. If sensory changes were not of the more usual stocking, shoe, sock, or glove distribution in the extremities, lateral (popliteal) involvement was more common than medial in the legs and ulnar than radial in the hands, though in three cases median-nerve compression was considered in the diagnosis. Occasionally there was numbness confined to one foot, with unilateral foot-drop, but in general the neuropathy was of symmetrical pattern, legs and feet being affected more than hands and arms, sensory findings occurring before and in excess of motor changes. The milder cases usually showed sensory changes only, though electromyographic examination in these cases showed a motor weakness also in the few where this investigation was done.

One interesting feature of the neuropathy was that the ankle reflexes were usually present even with extensive sensory loss. In only eight cases of our series were both ankle responses absent; it was striking how in rheumatoid patients with wasted calf muscles the ankle reflexes could normally be elicited with ease. As a rule, the ankle reflex was absent only if there was foot-drop on that side.

The earliest evidence of a neuropathy developing in rheumatoid arthritis is usually the patients' own unsolicited statement that something fresh, new, and unpleasant has happened to their feet, which feel different and are painful in a different way. Their unsolicited and voluntary statement was the earliest evidence of neuropathic change in most instances: in some cases physical signs were much less impressive initially than the patient's own firm statement of abnormality. Those of us who have had mandibular-nerve blocks for dental operations know how odd and abnormal the anaesthetized area feels even though the various forms of sensation can be roughly appreciated in that area. It is sobering to contemplate how often in the past patients must have made complaints almost diagnostic of this complication to their physicians, who, as this disorder was not an orthodox one described in the current textbooks on the subject, turned a deaf ear to them. The patient's account of these sensory changes is so completely unlike the usual one of the pain, stiffness, weakness, and swelling of his arthritis that it is extraordinary that they were ever confused.

Other Types of Neuritis in Rheumatoid Arthritis

In rheumatoid arthritis median-nerve compression in the carpal tunnel may occur, giving the signs and symptoms of this disorder; or large effusions in, or gross derangement of, certain joints may be associated with neuritis distal to them—for example, ulnar neuritis below a severely affected elbow. It is of interest that in one case under the care of Dr. A. G. S. Hill the initial disorder was diagnosed and treated as a carpal-tunnel syndrome with poor therapeutic response, only to be followed two and a half years later, after steroid therapy had been introduced, by a typical symmetrical rheumatoid neuropathy. In retrospect it is hard, on retaking the history, to differentiate the two, and it seems possible that all were manifestations of one disorder—that is, rheumatoid neuropathy. Similarly, in one of our patients a large effusion in the right elbow was associated with an ulnar neuritis on that side, but a more detailed examination on her next attendance revealed symmetrical sensory changes in the feet. Nevertheless, signs in the arm were so much more marked that Mr. David Evans was asked to transplant the ulnar nerve from its usual site to an area anteriorly where it could not be traumatized on the arms of chairs and table tops. At operation the nerve was exposed and explored. No thickening or adhesions were found, but the arcuate ligament between the two heads of flexor carpi ulnaris was thickened. This was incised for $\frac{1}{2}$ in. (1.3 cm.) and nothing more was done. This operation has given immediate and lasting relief and has cured the ulnar neuritis completely in the same way as a successful carpal-tunnel operation relieves the symptoms of median-nerve compression. Though these local causes for neuritis do occur in rheumatoid arthritis, in our experience they are rare, and when they do occur careful search should be made for signs of neuropathy elsewhere at the time and over several months subsequently.

Cervical spondylosis may occur in the more elderly patient and may confuse the picture in rheumatoid disease; for, although rheumatoid involvement of the cervical spine is not associated with narrowing of the foramina of Luschka, the later development of degenera-

tive changes may cause root pain referred down the arm. Though sensory changes may occur in the upper extremities with cervical spondylosis, simulating rheumatoid neuropathy, signs of upper-motor-neurone disease in the legs with extensor plantar response point to the correct diagnosis. Subluxation of one cervical vertebra on another with marked spondylolisthesis is recognized as a cervical complication of rheumatoid arthritis, and the resultant quadriplegia is one of the most unpleasant complications of this disease and one of the hardest to treat. One of our patients, ten years ago, while at convalescent home developed contracture deformities due, not to her rheumatoid disease, but to the insidious development of subacute combined degeneration of the cord. Other conditions which may be encountered are neuritis associated with malignant disease, with alcohol, with diabetes mellitus, or with amyloidosis.

It is worthy of note that although the female : male ratio in rheumatoid arthritis is about 2.5 : 1 in this country, both in this series and in that of Steinberg (1960) the sex incidence of rheumatoid neuropathy is about unity—that is, more male patients get this complication than do females. It is of further interest that the usual sex incidence in other types of peripheral neuritis is predominantly male, Rose (1960) giving the male : female ratio as 3 : 2. There seems to be no adequate explanation for this predominance of males in neuropathic disorders.

Pathology

Seven deaths have occurred in this series—four of our own patients, one (Case 5) of Drs. West and Newns in Sheffield, and two of Drs. Mason and Tegner at the London Hospital. These last two cases have already been reported (Mason and Steinberg, 1958). Four necropsies have been done on patients with rheumatoid neuropathy at the Westminster Hospital. Extensive arteritis had been found in one male case, previously reported by us (Hart *et al.*, 1957). The clinical and necropsy findings in five fatal cases are given in the accompanying Table.

Case 1.—This patient was a man of 55 whose clinical course was marked by extensive neuropathy, episodes of left ventricular failure, and necrotic vascular lesions of the fingertips, as described by Bywaters (1957). During the last four weeks of life the neuropathic symptoms in his hands improved greatly, though he deteriorated in other ways; and, before his death, examination of the hands revealed a diminished vibration sense of the fingers and diminished two-point discrimination as the only abnormalities. At necropsy there was obliteration of the pericardial sac by a fibrinous pericarditis. The surface of the heart was red, and nodules were seen along the anterior descending branch of the left coronary artery. There was atheroma of all the coronary arteries. Histologically, arteritis was found in the small arteries of the heart, pericardium, lungs, and peripheral nerves in the feet. Different grades of arteritis were found: the most mild consisted of perivascular infiltration with lymphocytes, but some vessels showed fibrinoid necrosis, periarteritis with infiltration by different types of cell, and aneurysmal dilatation of the vessel walls typical of polyarteritis nodosa. Section of peripheral nerves in the right leg showed obvious demyelination and arteritis of the vasa nervorum. The right median nerve was apparently normal histologically. It is of interest that, during life, biopsies of skin, muscle, and small arteries did not show any abnormality.

Case 2.—A man aged 43 had clinically a myocardial infarct eight weeks before his death, which was due to bronchopneumonia. He had more gross signs of peripheral neuropathy at death than any other patient in our series. At necropsy the pericardial cavity contained little fluid, but there was no fibrinous pericarditis. An area of fibrosis representing healed infarction was found on the posterior wall of the right ventricle. A little nodule was seen on the artery supplying the infarcted area, which was suggestive but not diagnostic of polyarteritis nodosa. There was a purulent bronchitis and extensive confluent bronchopneumonia. No other significant macrocytic abnormality was seen. Histologically, evidence of arteritis was seen in two of the smaller vessels of the coronary tree. In the first a segment of muscle coat was replaced by fibrous tissue and the internal elastic lamina was fragmented. In the second there was a form of fibrinoid material infiltrated by young fibroblasts and surrounded by granulation tissue. Active and healed arteritis was seen in the liver. It was difficult to be certain whether a form of arteritis in the lungs was due to his rheumatoid disease or to the terminal bronchopneumonia. Arteritis was seen in one small splenic vessel and in one medium-sized artery in the adrenal capsule. Most interesting of all, however, were the nerves: Sections of nine peripheral nerves of arms and legs showed no abnormality, either arteritis or demyelination. An isolated

Clinical and Necropsy Findings in Five Fatal Cases

Case No.	Sex and Age	Duration R.A.	Duration Neuropathy	Nodules	R.W. D.A.T.	Duration Steroid Therapy	Cause of Death	Cardiac Findings	Arterial Lesions	Neurological Findings	General Comments
1	M 59	6 years	9/12	++	1/256	1 year abruptly stopped	Acute left ventricular failure	Nodules on coronary arteries. Fibrinous pericarditis	Diffuse arteritis and periarteritis	Arteritis + and demyelination	—
2	M 43	12 ,,	15/12	++	1/256	7/12 stopped abruptly	Coronary thrombosis. Bronchopneumonia	Arteritis. Coronary thrombosis	Scattered arteritis	9 nerves from extremities, all normal	Multiple areas of fibrosis suggestive of repair
3	F 58	4 ,,	2/12	+	1/128	4 years	Complicated R.A. with hypercortisonism	Pan- and pericarditis	Arteritis of 1 peripheral nerve only	Arteritis vasa nervorum in one area	Marked signs of hypercortisonism. Multiple fractured ribs. Collapsed vertebrae
4	F 56	14 ,,	2/52	+	1/128	7 ,,	Coronary thrombosis	Right coronary artery thrombosed	Nil	Nil	Previous perforated double peptic ulcer and staphylococcal septicaemia
5	M 46	16 ,,	2 years	—	—	3 ,,	Pulmonary artery thrombosis. Intestinal bleeding from peptic ulcer. Bronchopneumonia	Adherent pericardium only	,,	,,	Pyaemia

arteritic lesion could easily have been missed, but it might be thought that demyelination would have been demonstrable distally.

Case 3.—A woman aged 58, a nodular rheumatoid case, developed mild sensory neuropathy of the legs only a few weeks before her death. Again an adherent pericarditis was found, with a few haemorrhages immediately below the visceral layer of the pericardium. The lung bases and liver were congested. Pancarditis was shown histologically, with changes of activity and healing in different areas. The myocardium was infiltrated with chronic inflammatory cells and contained numerous small paravascular areas of acellular collagen. The coronary vessels themselves were normal. One section of a small cutaneous nerve of the foot showed a grossly thickened wall of its nutrient artery, with narrowing of the lumen. The wall was infiltrated with lymphocytes; this was the only example of a true arteritis seen in all the sections examined.

Case 4.—The death of this patient occurred half an hour after a large coronary thrombosis. She had developed symptoms and signs of sensory peripheral neuropathy on the lateral border of the right foot two weeks previously. At necropsy, careful examination of her viscera failed to demonstrate any evidence of arteritis, though the right coronary artery was completely plugged by thrombus. The nerves in the leg were dissected out from the sciatic nerve via the lateral popliteal nerve and then down through the cutaneous nerves to their many small ramifications. Examination of 50 sections from largest to smallest nerves failed to show either arteritis or demyelination.

Case 5.—The findings in this case are similar to those in Case 4. The patient had marked signs of motor and sensory neuropathy in the feet and legs, and died after pulmonary thrombosis and intestinal bleeding from a gastric ulcer. No organ, including sections of nerves, showed any arteritis, apart from some perivascular round-celled infiltration in the dermis.

It will be noted that three of these five fatal cases died cardiac deaths—two from coronary thrombosis and one from cardiac failure. It is ironic that the first two patients had been reasonably well for some years on aspirin but later worsened, were transferred to steroid therapy, and deteriorated after its sudden withdrawal in each case. Cases 3 and 4 were active progressive patients with hypercortisonism, the latter having perforated a gastric ulcer and been cured of staphylococcal septicaemia previously. In all five cases steroid therapy clearly contributed to the general condition and downhill course. The scanty or absent findings in the peripheral nerves in the last three cases are of interest, for these patients all showed abundant clinical evidence of neuropathic disorder at the time of their death.

Discussion

In a search for other causes for the neuropathy we found no evidence in our cases of any other aetiological agent such as amyloidosis, porphyria, diabetes, avitaminosis, intercurrent infection, or heavy metal poisoning. On the existing evidence most authors feel that the neuropathy is probably due to vascular lesions, which are commonly seen to co-exist. Johnson *et al.* (1959) found that 14 out of 138 patients treated in 1957 with adrenocortical steroids developed peripheral neuropathy. Of these 14, 11 had subcutaneous rheumatoid nodules; the D.A.T., or Rose–Waaler, test was positive in 13 and the L.E. cell absent in the 13 cases where this test was performed. In six cases steroid therapy had been uninterrupted, five had occurred one to five months after it had been discontinued, and in three cases it had been stopped and restarted. In their three fatal cases polyneuropathy preceded gangrene and multiple systemic manifestations, being more severe and extensive than in the survivors.

Epstein and Engleman (1959) reported nine cases of typical rheumatoid arthritis in which severe vascular occlusive lesions and peripheral neuropathy developed. All nine patients were receiving steroids, usually prednisone or prednisolone, and had been on such therapy for from one and a half to five years. All had severe rheumatoid disease, subcutaneous nodules, large amounts of circulating rheumatoid factor, and ischaemic skin change. In four cases an arteritis was seen in biopsy specimens, in four it was not. Sokoloff and Bunim (1957), Mason and Steinberg (1958), Steinberg (1960), and others have also reported similar cases. Irby *et al.* (1958) reported 6 cases that were on, or had been receiving, steroid therapy. All were long-standing severe cases. Examination of the cerebrospinal fluid was made in all cases and was normal except for an elevated protein (90 mg.) in one. Radnai (1953) emphasized the importance of vascular changes in the development of neuropathy in rheumatoid arthritis, and Slocumb (1953) drew attention to the "panangiitic and panmesenchymal reactions" which occurred on reduction of steroid dosage in this disorder.

Kemper *et al.* (1957) reported that of 52 rheumatoid patients studied at necropsy 38 had received no cortisone. None of these developed generalized lesions of polyarteritis nodosa, whereas of the cortisone-treated patients four did so, three showing signs of neuropathy. In reviewing the literature on this subject they consider that the vascular changes observed in rheumatoid arthritis fall into three groups: (1) perivascular or adventitial accumulation of leucocytes, plasma, or other cells, with no noticeable necrosis; (2) subacute arteritis with histiocytic and lymphocytic infiltration through all layers of the vessel wall, without necrosis, but possibly with some exudation of fibrin and swelling of collagen; and (3) lesions of acute arteritis with cellular infiltration and necrosis of the vessel wall—a necrotizing angiitis. These workers thought that this suggested that in certain susceptible patients with rheumatoid arthritis the administration of cortisone might precipitate changes in the third group, and there is a good deal of secondary evidence that this may occur. The fact, however, that approximately one-third of our patients had had no steroid therapy at the time of the development of the neuropathy suggests that this may and does occur as a true primary or "rheumatoid" neuropathy. We may therefore postulate three groups:

1. Rheumatoid neuropathy occurring in the absence of steroid therapy or any other known agent.

2. Neuropathy occurring after reduction or cessation of steroid dosage. In this case it is possible that a polyarteritis may flare up and occlusive lesions occur in relation to nervous tissue.

3. Neuropathy occurring with constant steroid dosage. In these cases fluctuations in the underlying disease activity, or additional trauma or other aggravating factors, may well play a part. In several of the case-histories some traumatic experience did occur within a few weeks of development of the neuropathy. In this last context the following case-history is of interest.

A married woman aged 35 had for some years been performing on the music-halls as a contortionist. The onset of acute rheumatoid arthritis necessitated a change in the act, and she became an assistant to her husband as

he performed as conjurer. She was by now on prednisolone, 15 mg. daily, and was keeping relatively well on it, when she heard that a medically unqualified hypnotist was curing patients by hypnotizing them out of their arthritis. Unhopeful, but persuaded by a friend (of the hypnotist), she submitted herself to the process; but the hypnotist, unable to procure a hypnotic trance, proceeded to give her "trilene" anaesthesia on three separate occasions. Her arthritis became rapidly worse, and one and a half hours after the third unsatisfactory anaesthetic she became febrile and ill. Next day she felt completely exhausted and noticed numbness of her fingers. Her feet and ankles felt numb and "prickly," but were also unduly sensitive and painful. In her act, that night, she fumbled with the playing-cards and could not properly use her right thumb. When examined 11 days later her hands had returned to normal, but sensory changes remained over short-sock distribution in both feet.

We have seen other transient cases of this nature. It is possible that traumatic factors flared up a latent arteritis which under ordinary conditions and under suppressive steroid therapy had remained quiescent. The following case-history demonstrates the same transient type of neuropathy, in this instance precipitated by withdrawal of steroid therapy.

A man aged 63 had severe active chronic progressive rheumatoid arthritis of 10 years' duration. After two years on steroid therapy, prednisolone was very gradually reduced over a period of four months from 15 to 5 mg. daily. He then developed paraesthesiae over feet and heels. Prednisolone was discontinued completely three weeks later, and one week afterwards he lost the power of dorsiflexion in one foot, paraesthesiae became more pronounced, and sensation was impaired over both feet. Three days later power returned and the sensory symptoms gradually abated.

This case appears to be a steroid-withdrawal syndrome in miniature followed by rapid improvement. Such transient cases are undoubtedly more often missed than noted; in this particular instance the patient was an in-patient and, because of steroid withdrawal, was under particularly close daily supervision.

Why peripheral neuropathy occurs in rheumatoid arthritis is still unknown, and before accepting it as due to an inflammatory arteriopathy one might consider the evidence against this thesis. If we compare the type of neuropathy seen in our rheumatoid patients with that described by Lovshin and Kernohan (1948) in polyarteritis nodosa we find the following differences:

Polyarteritis Neuropathy	*Rheumatoid Neuropathy*
1. Usually asymmetrical ..	Usually symmetrical
2. Essentially motor	Essentially sensory
3. None sensory only	Many sensory only
4. If clinically present histological findings invariably present	No histological findings in some cases clinically severely affected

If rheumatoid neuropathy were entirely due to an arteritis one might perhaps expect a greater similarity in these two groups. Mononeuritis multiplex occurs in rheumatoid arthritis as it does in idiopathic polyarteritis nodosa, and then it tends to be in ulnar or lateral popliteal distribution. This is also the more common distribution in symmetrical rheumatoid neuropathy, suggesting that the asymmetrical pattern of the one is merely a milder variant of the other, the disease being, as it were, "spread thin." We have seen several cases progress from the patchy type to the more symmetrical over a period of several months. Why rheumatoid neuropathy tends to be symmetrical if it be due to an arteritis is obscure; it suggests a very diffuse low-grade silent involvement of vessels picking off the longest nerve fibres. The work of Lewis *et al.* (1931) demonstrated that the sensory fibres are more sensitive to ischaemic changes. The alternative explanation is that the neuropathy occurs as part of the rheumatoid illness and is not directly due to an arteritis.

It is of interest here to compare diabetic and rheumatoid neuropathy. Both were overlooked for many years, and both were then ascribed to vascular damage; now the cause of diabetic neuropathy is admittedly unknown. Both affect feet more than hands, are sensory rather than motor, and are symmetrical rather than asymmetrical, with vibration sense much impaired; but there the similarities cease. It is in our experience rare for diabetes and rheumatoid arthritis to coexist, considering how common both conditions are.

Summary and Conclusions

Peripheral neuropathy occurring in rheumatoid arthritics is reported in 42 cases (18 male and 24 female). This relatively high incidence in males has been noted in other reported series of cases, and is in line with the incidence in other types of peripheral neuritis.

Of these 42 patients, 15 had had no steroid (cortisone) therapy within three years of onset of the neuropathy and 12 had never previously received such therapy at any time. We consider the condition a part or a complication of rheumatoid arthritis and have therefore termed it "rheumatoid neuropathy."

The worst cases and all the fatal ones with one exception were treated with steroid, as were the great majority of the reported cases in the world's literature. Sudden withdrawal or changing of steroid treatment may precipitate this complication.

The neuropathy is usually symmetrical and is primarily sensory, motor findings occurring in the more severe cases. Feet and legs are more often affected than hands and arms.

Rheumatoid neuropathy occurs more commonly in patients with nodules and advanced rheumatoid disease, usually with a high-titre D.A.T. (Rose–Waaler test). Vascular necrotic finger lesions may co-exist.

In some cases the finding of a diffuse arteriopathy at necropsy suggests that the probable cause is an arteritis of the vasa nervorum, and at present this is generally accepted as the most likely explanation. It fails, however, to explain adequately all cases coming to necropsy in our series nor the essential differences in the clinical pictures of these cases and those previously reported with neuropathy as part of idiopathic polyarteritis nodosa.

Though mild cases do occur, many recovering spontaneously, rheumatoid neuropathy should in general be regarded as a serious complication and one carrying a bad prognosis. No form of therapy has to date been found to be effective.

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NEUROPATHY IN RHEUMATOID DISEASE

BY

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Over the past few years it has become increasingly obvious that rheumatoid arthritis is a generalized disease, and during this time the systemic manifestations have been described with increasing frequency. In the past six years at least ten communications have described patients with rheumatoid arthritis in whom there was evidence of a neuropathy usually peripheral. Previous to this, clinical reports of neuropathy were rare, and the present increase appears to have coincided with the introduction of steroid therapy. Pitres and Vaillard (1887) found pathological changes in the peripheral nerves of three rheumatoid patients at necropsy. Bannatyne (1898) noted peripheral neuritis in a number of cases and described pathological changes involving the blood-vessels of the nerves. Freund *et al.* (1942) reported changes in the peripheral nerves in five patients seen at necropsy, and Morrison *et al.* (1947) found similar changes in 26.

Twenty cases of rheumatoid arthritis with peripheral neuropathy have been observed at the London Hospital or Chase Farm Hospital. Two of these were included by Hart *et al.* (1957) in their series, and are not discussed here. Six were previously reported elsewhere (Mason and Steinberg, 1958), but the survivors have been followed up and all are included in the present series.

Clinical Details

All 18 patients are classified as definite by American Rheumatism Association criteria (Ropes *et al.*, 1956), though L.E. cells have been demonstrated in three at one time or another.

Table I gives brief clinical details of these patients. The sex incidence is equal. Though different series show varying ratios, nine other series, totalling 56, show roughly equal sex incidence when added together

TABLE I.—*Clinical Data of 18 Patients with Rheumatoid Arthritis who Developed Neuropathy*

Sex	Males, 9; females, 9	Active disease	18
Age	27–71 years (average 55)	Nodules	7
Duration	1–17 ,, (,, 5)	Serology positive	14
		Associated with flare	12

Present Condition

Dead	5 (within 1 year of onset)
Bedbound	5
Varying degrees of disability	8

TABLE II.—*Sex Incidence of Neuropathy in Various Series*

	Males	Females
Ball (1954)	1	1
Kemper *et al.* (1957)	2	1
Sokoloff and Bunim (1957)	1	1
Hart *et al.* (1957)	6	4
Irby *et al.* (1958)	5	1
Mason and Steinberg (1958)	3	3
Vignon and Durant (1958)	1	1
Johnson *et al.* (1959)	5	12
Epstein and Engleman (1959)	3	5
	27	29

(Table II). This is in contrast to the rest of rheumatoid patients, where females predominate by at least two to one.

The ages of the patients ranged from 27 to 71 years, with an average of 55. Disease duration was from one to 17 years, with an average of five. All the patients were suffering from active disease at the time of the onset of the neuropathy. Nodules were present in seven (39%). This is in contrast to Johnson *et al.* (1959), who found an incidence of 71% and Epstein and Engleman (1959), who found 100%. Either the Rose or the latex test was positive in 14 (77%). It is not possible to draw any conclusions from the titres, as the two tests are different, more than one laboratory was involved, and the technique was changed during this period. Epstein and Engleman (1959), however, noted that all their eight patients had very high titres with the F.II haemagglutination test. The neuropathy was associated with a flare in 12 cases (66.6%). This in itself may not be significant, because the flare may bring the patient under closer observation and be responsible for changes in therapy.

At present five patients are dead, all within one year of onset, and three within one month. All of these patients were on steroids or A.C.T.H. (see Table III). Five are more or less bedbound owing to the neuropathy; the remaining eight are a mixed group, but it must be stated that for five it is still early days.

TABLE III.—*Details of the Five Patients that Died*

No.	Sex and Age at Onset	Duration of R.A. at Onset of Neuropathy	Time between Onset of Neuropathy and Death	Cause
2	F 64	6 years	9 months	Pyrexia and increasing dyspnoea for which no cause could be found. It was decided to withdraw steroids, after which patient died. ? adrenal failure
3	M 71	2 ,,	1 month	Chest pain and dyspnoea. Presumed coronary thrombosis
4	F 64	1 year	2 weeks	Acute bronchopneumonia with multiple abscess formation. Post-mortem: polyarteritis of myocardium, kidney, sciatic nerve
6	M 54	4 years	6 months	Tuberculous bronchopneumonia. Post-mortem: polyarteritis sciatic and femoral nerves
13	M 57	1 year	1 month	Sudden death. Coroner's post-mortem: death due to myocarditis and atherosclerosis

TABLE IV.—*Features of the Neuropathy*

Distribution		Sensory	18	Course	
Lower limbs	12	Motor:		Dead	5*
Upper ,,	1	Clinical	8	Recovered	1
Upper and lower limbs	5	Electrodiagnosis	4 more	Improved	1
Bilateral	13			Progressive or static	11
Symmetrical	8				18

* Neuropathy improved before death in one case.

Neuropathy, therefore, in rheumatoid arthritis is a serious prognostic finding.

The details of the neuropathy are shown in Table IV. The lower limbs alone were affected in 12 patients, both upper and lower limbs in five patients, and one upper limb alone in one patient. This was a man who had extensive arteritic phenomena affecting the hand, with evidence of sensory loss.

Of the five cases in which both upper and lower limbs were affected, in three the legs were more severely involved and in the other two the involvement appeared to be equal. The condition was bilateral in 13 but strictly symmetrical in only eight of these, for though the same areas, more or less, were always involved, in five the degree of involvement was strikingly different. This was the position at the time of the analysis, for the distribution changed from time to time. Objective sensory changes were present in all the patients. In addition eight patients showed motor weakness.

Electrodiagnosis was performed on four patients who at that time showed no clinical evidence of motor involvement, and in every case there was evidence of a motor neuropathy; the intensity duration curve showing denervation, or the electromyograph a reduced interference pattern with long-duration polyphasic units. In one case these changes were followed in three months by a severe unilateral foot-drop. Even when motor changes are obvious clinically, electrodiagnostic tests reveal that these may be more extensive than is apparent. In every case sensory symptoms preceded motor symptoms—the latter, when they occurred, following at varying intervals of time. The longest interval in our experience is five months.

All the patients presented with tingling, burning, and numbness of the extremities, the burning sensations being so severe in some cases as to require strong analgesics. These sensations were often the patient's chief complaint. Muscle pain was also present, and, as in other forms of peripheral neuropathy, the calves could be extremely tender. In one patient hyperaesthesia was one of the most severe symptoms. Loss or impairment of sensation to pinprick, temperature, and light touch was present in all cases and more or less followed the paraesthetic areas. The deep reflexes were usually preserved except for the ankle-jerks in seven of the cases. Loss of position sensation was variable, and was usually confined to the toes. Loss of vibration sense, which was often more widespread than other changes, occurred in 10 cases. The sensory changes alone were in some cases sufficient to account for the impaired functional capacity.

When present, motor weakness was definite and was always responsible for some of the symptoms, though they could be overshadowed by the sensory symptoms. In every case the motor changes were confined to the lower limbs. In six these were manifested as foot-drop, either unilateral or bilateral.

It is important to consider the steroid history of these patients. Only three had never been on steroids, and these had minimal signs; five were on continuous steroid dosages; and in 10 there appeared to be a definite relationship to either initiation or alteration of steroid therapy.

TABLE V.—*Relationship to Steroids*

Case 1. Prednisolone 15 mg. daily 1 year. Neuropathy 3 months after withdrawn
,, 3. Cortisone 75 mg. daily 1 year. Changed to prednisolone 20 mg. daily 4 months. Abruptly withdrawn 3 months before onset
,, 4. A.C.T.H. 40 units daily 1 week, then stopped. Neuropathy within 4 weeks
,, 6. Cortisone 75 mg. daily 1 year. Prednisolone 15 mg. daily for 2 months before onset
,, 7. Prednisolone 10 mg. daily 10 months. Changed to triamcinolone 8 mg. daily 3 months before onset
,, 8. A.C.T.H. 1 year, followed by triamcinolone for 6 months, interrupted for 7 days. Prednisolone for 4 days before onset
,, 9. Prednisolone acetate 100 mg. weekly for 2 months prior to onset
,, 11. Prednisolone 15 mg. daily 1 month before onset
,, 13. A.C.T.H. 80 units for 3 days, reduced to 60 units. Reduction accompanied by neuropathy
,, 18. Cortisone 50 mg./25 mg. alternate days for 7 years. Withdrawn under A.C.T.H. cover. Neuropathy within 3 days of stopping cortisone. Still on A.C.T.H.

Table V shows this relationship. Thus in Cases 1, 3, and 8 the neuropathy followed the interruption of prolonged steroid therapy; in Cases 9 and 11 it followed the introduction of steroids in Cases 6 and 7 a change in steroids, in Case 4 A.C.T.H. initiation and withdrawal, in Case 13 A.C.T.H. initiation and reduction; and in Case 18 it followed cortisone withdrawal under an A.C.T.H. cover while still on A.C.T.H.

Thus 15 out of 18 patients were or had been on steroids and in 10 there appeared to be a direct connexion with such therapy. This does not preclude a connexion between the other five on continuous steroid dosage. This association of neuropathy with steroid therapy has been noted in other series, but it is by no means constant. Robinson *et al* (1953) showed four cases of rheumatoid arthritis that developed neuropathy; only one had never received steroids or A.C.T.H. Neither of the two cases described by Ball (1954) was on cortisone before the onset of the neuropathy; all cases of Kemper *et al.* (1957) had been, as had the two described by Sokoloff and Bunim (1957), one of which was a case of cranial neuropathy. Five of the 10 cases of Hart *et al.* (1957) had never received steroids, but in three the neuropathy developed within one month of discontinuing them.

In three series described by Irby *et al.* (1958), Johnson *et al.* (1959), and Epstein and Engleman (1959)

all the patients were, or had been, on steroids. In eight of Johnson's 17 patients neuropathy followed interruption or cessation of steroid therapy; all of his patients showed evidence of hypercortisonism prior to the onset of the neuropathy. Evidence of hypercortisonism was not prominent in this series; one patient had evidence of mild osteoporosis of the spine, one had pathological fractures of the humerus and femur one year before neuropathy, and one developed purpuric haemorrhages at the time of the neuropathy. Apart from this the other patients showed some mooning of the face or gain in weight.

TABLE VI.—*Associated Features*

Lupus erythematosus cells	3
Digital arteritis	5
Other evidence of arteritis	1
Lung changes	4
Other systemic disturbance (i.e., fever, splenomegaly, albuminuria)	4

Table VI shows the associated features of these patients. L.E. cells were detected in the serum of three patients at one time or another. All three were males. In one they were found on two occasions three years prior to the onset of the neuropathy; in one, a year after the onset of the neuropathy (this patient also had evidence of digital arteritis); and in the third they were found after the neuropathy had remitted, but at a time when he was having fresh digital arteritic phenomena. This patient also had *x*-ray changes of the rheumatoid lung. Five patients had evidence of digital arteritis as described by Bywaters (1957). The time relationship of the onset of the digital arteritis to the neuropathy was very variable. One patient had post-mortem evidence of polyarteritis nodosa affecting the kidney and myocardium. Four patients had *x*-ray changes in the lung fields thought to be due to the rheumatoid disease.

No treatment seemed to affect the course of the neuropathy in these patients, and this is the view also expressed in other series. Steroids did not control the condition, though in two patients who were not on steroids at the onset of neuropathy this did improve when they were employed. It would appear wiser, however, to avoid too violent a fluctuation in the steroid dosage when a neuropathy does occur.

Aetiology

The evidence seems to suggest that neuropathy in rheumatoid disease is secondary to arteritis. In two cases that came to necropsy in this series there was evidence of polyarteritis nodosa affecting the peripheral nerves.

This finding of an arteritis has been noted in all the series so far reported, but the exact changes appear to cover a wide spectrum. Thus Robinson *et al.* (1953) found arterial changes which differed qualitatively from classical polyarteritis nodosa; Ball (1954) found evidence of polyarteritis nodosa; in the one case of Hart *et al.* (1957) that came to necropsy there was widespread arteritis, including fibrinoid necrosis; and Johnson *et al.* (1959) found post-mortem evidence of arteritis in three cases, in one of which the changes were those of classical polyarteritis nodosa. Further support for a vascular basis of the neuropathy is that five of our patients also had evidence of digital arteritis. This again has been the experience with other series. On the other hand, it must be remembered that arteritis is seen in the absence of neuropathy and may simply be a feature of rheumatoid disease. Thus Cruikshank (1954) found the nerves to be one of the most common sites of arteritis; and Sokoloff and Bunim (1957) detected arteritis of the nerves in two patients (Nos. 3 and 5) in in whom there was no clinical evidence of neuropathy.

Discussion

It is important to discuss neuropathy in rheumatoid disease against the wide background of vascular changes that may occur. It seems more than likely that there has been a true increase in these changes over the last few years, and this has coincided with the introduction of steroid therapy. Clinically they were hardly mentioned and post-mortem evidence of arteritis was equally rare. It is of course possible that they were present but were missed; and we know, once something is described, how obvious its presence is to all of us.

Freund *et al.* (1942), who reported characteristic changes in the perineurium, calling the condition nodular rheumarthritic polyneuritis, made no reference to any vascular change. Baggenstoss and Rosenberg (1943), reporting on 30 post-mortem cases, found no changes in the blood-vessels though these were looked for.

What is the relationship between steroid therapy and arteritis, and hence neuropathy? In most patients steroid therapy has been used, but these changes may occur in the absence of steroids. Though none of the post-mortem cases described by Cruickshank (1954) had been on steroids, the changes appear to be more severe in the steroid-treated cases. Kemper *et al.* (1957), reporting on 52 post-mortem cases, found evidence of vasculitis in 12. Four of these who had received cortisone had changes similar to polyarteritis nodosa. He concluded that in certain susceptible patients with rheumatoid arthritis cortisone may precipitate a diffuse necrotizing arteritis.

Epstein and Engleman state that the association of rheumatoid arthritis, subcutaneous nodules, and the presence of large amounts of rheumatoid factor in the serum may constitute a relative contraindication to the use of adrenocortical steroid therapy.

It may be that the fact that most of these cases were on steroid therapy is an indication of the severity of the rheumatoid process rather than the cause of the arteritis and neuropathy. It seems that these manifestations may be provoked by sudden changes in steroid therapy, and Slocumb (1953) drew attention to the panangiitic and panmesenchymal reactions which may occur after cortisone reduction.

Summary

Eighteen cases of rheumatoid arthritis with peripheral neuropathy are described. In 15, steroids or A.C.T.H. had been used, and in 10 there appeared to be a direct association between changes in such therapy and the onset of the neuropathy. Five patients died within one year of the onset of the neuropathy, and all were on steroids or A.C.T.H. No treatment appeared to affect the course of the neuropathy. Digital arteritis occurred in five patients, and there was post-mortem evidence

of arteritis of the peripheral nerves in two cases. A diffuse arteritis may be the cause of the neuropathy.

The onset of peripheral neuropathy is of poor prognostic import in rheumatoid disease.

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SOME OBSERVATIONS ON THE AETIOLOGY OF BREAST ABSCESS IN THE PUERPERIUM

BY

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The purpose of this paper is to shed light on the ways in which breast abscesses arise in mothers who suckle their infants. The observations were made in a busy modern obstetric department throughout a period in which there was a rising incidence of infection with an unusually virulent type of staphylococcus (phage-type 80).

In 1957 an outbreak of breast abscesses occurred in epidemic form. Owing to the geographical position of Southampton all mothers who developed a breast abscess needing incision were seen either at the General Hospital or at the casualty department of the only other hospital in the city. These circumstances provided, therefore, an unusual opportunity to follow up infections which developed after mothers had been discharged from the maternity wards.

Much evidence has been produced of the early colonization with *Staphylococcus aureus* of babies born in maternity hospitals, and it has been shown that there is little correlation between the type of organisms found in the nares or vagina of mothers and in the nares of their infants (Barber *et al.*, 1953; Cook *et al.*, 1958). Reports have been made on the particular aspects of the mechanism of this colonization, and it was found that all full-term babies were colonized with staphylococci in the first few days of life unless protective measures were adopted (Hurst, 1957; Cook *et al.*, 1958). It appeared also that most infants acquired their staphylococci from the nursing staff or from other babies rather than from their mothers (Knott and Blaikley, 1944; Edmunds *et al.*, 1955).

Duncan and Walker (1942) noted that *Staph. aureus* of the same type was isolated both from the milk of nursing mothers and from the rectum and throat of their babies in a high percentage of cases. They suggested that staphylococci were deposited on the mothers' breasts by the babies' noses. Sensitivity tests showed that in most cases babies' noses and mothers' breasts bore like staphylococci.

Further evidence supporting this theory was provided by Cook *et al.* (1958). They investigated the acquisition of *Staph. aureus* by newborn babies and acquitted the mothers as a possible source of infection.

Duncan and Walker postulated a continuous process of infection from baby to baby via the ward environment and thence transference, through suckling, to the breasts of mothers. The staphylococcus then multiplied in the breast milk and was returned again to the baby, sometimes in massive doses though apparently of low pathogenicity. They also found that breast milk was infected after 24 hours of the puerperium but not before delivery. In the milk of the mothers of 28 stillborn infants who did not suckle there was a much smaller incidence of staphylococci. Thus there seemed to be a definite correlation between suckling and milk infection.

More evidence of the importance of the babies themselves as carriers was provided by Colbeck (1949), who investigated 160 cases of breast abscess in Winnipeg hospitals in 1949, taking nose and throat swabs from the babies. He stated that it is possible that infected nasal secretions may pass to the back of the throat and into the baby's mouth and so be regurgitated into the terminal mammary ducts during suckling. Infection of the mothers' nipples by babies' nasopharyngeal organisms is inevitable if breast-feeding is practised. No "breast toilet" can prevent this, and the customary nipple treatment is more likely to introduce a further infection to the mother and infant than to eliminate it. Colbeck thought that if a mother developed a breast abscess, breast-feeding should be stopped. He raised the possibility of lung abscess occurring in the infant through aspiration of infected milk.

Wysham *et al.* (1957) showed that the infants themselves were the major source and reservoir of pathogenic staphylococci. They reported their investigations on 117 mothers and their babies and postulated that staphylococci from babies' mouths may be aspirated into the mammary ducts during feeding when the negative pressure which is created within the ducts at suckling is released. They showed that staphylococci in the throats of babies could pass through the hole in a rubber teat and contaminate the contents of a bottle during normal feeding.

Present Investigation

This survey includes all cases of breast abscess known to have occurred after confinements in the maternity wards of one hospital during 1957. The term "breast abscess" is used to signify definite abscess formation which required surgical incision or discharged spontaneously.

The obstetric unit is situated in a separate building from the main hospital and was staffed solely by trained and student midwives, so that there was little possibility of cross-infection from general medical and surgical wards.

It was the practice in the maternity wards for normal babies to be nursed alongside their mothers. Premature babies and those born by abnormal delivery were removed from the labour ward or theatre straight to the nursery until they were considered fit to join their mothers. No babies were bathed during their time in hospital. There was an isolation department which was self-contained and was staffed by midwives who did not work either in the labour or the post-natal wards.

As soon as the presence of *Staph. aureus* phage-type 80 was discovered, whether it was being merely "carried" or whether it was causing frank infection, both mother and child were transferred to the isolation unit and barrier-nursed in cubicles.

Nose and throat swabs were taken from all midwives at least once weekly. Those who were found to be carriers of phage-type 80 organisms were excluded from the labour and post-natal wards Chlorhexidine diacetate ("hibitane") cream was introduced into the hand-washing routine in all wards.

Incidence of Breast Abscess.—During the year 1957 there were 1,732 admissions to the maternity wards. As there was no other obstetric department in the area, which served a population of 200,000, beds were in constant demand both for booked cases and for the unduly large number of emergency admissions—240 (13.9% of total). During the year 37 mothers (2.1% of total admissions) developed breast abscess. Two of these were emergency admissions. Towards the end of 1956 there was an outbreak of salmonella infection in the obstetric department, and no admissions were permitted for seven weeks while thorough cleansing of the wards was undertaken. Patients were admitted again at the end of December, 1956. At first there was a low incidence of infection of mothers and babies, which increased steadily throughout the first six months of 1957. The number of abscesses developing in each month rose to a peak in July and then diminished.

Obstetric History.—Of the 37 patients in the series, 26 were primiparae and 11 multiparae. The average age of the mothers was 26.0 years (range 18–46 years). 90% of the mothers were delivered within 24 hours of admission, and the admission-delivery interval ranged from less than one day to three days. 29 patients had normal deliveries, three were delivered by caesarean section and one by forceps, and there were two sets of twins and two breech deliveries. One macerated foetus was born. There were five cases of post-partum haemorrhage, including two which needed manual removal of the placenta.

Suckling.—35 mothers suckled 37 babies. In only two patients who developed a breast abscess in this series was the baby not put to the breast. Of these, one patient developed a superficial breast abscess before delivery and one was delivered of a macerated foetus and lactation was suppressed.

Type of Feeding on Discharge from Hospital.—19 mothers went home from hospital breast-feeding their babies, 2 used breast and complement, and 15 used artificial feeding. There is evidence, however (Tytten *et al.*, 1958), to show that many mothers who breast-feed infants in hospital change to artificial feeding soon after reaching home. Bottle-feeding was officially encouraged in approximately half of the patients in the last three months of 1957 because of the concern caused by the frequency of breast abscess in mothers who breast-fed their babies.

Length of Stay in Hospital After Delivery.—This varied from 2 to 32 days (Table I). The policy of early discharge from the hospital was determined by the great demand for the limited number of beds.

TABLE I

Days:	0–5	6–10	11–15	16–20	21–26	27–32
No. of mothers ..	1	22	9	3	0	2

Previous Feeding History.—The 11 multiparae had borne 13 children previously: nine of these had been satisfactorily breast-fed and four artificially fed. None had had previous breast abscesses.

Breast Disorders While in Hospital.—The great majority of patients (25) had developed no symptoms or signs of breast disorders before they were discharged home (apart from some transient engorgement in the early stages of lactation). Nine patients had cracked nipples (unilateral in six), three had acute mastitis with a cracked nipple, and three had acute mastitis without a cracked nipple. In all except three cases the mastitis resolved before the patient left hospital. Antibiotics were used in four cases (tetracycline or chloramphenicol). Breast abscess subsequently developed on the same side as that on which these earlier abnormalities had occurred. In 18 patients an abscess developed in the right breast, in 12 in the left breast, and 7 had bilateral breast abscesses.

Antibiotics Given After Discharge from Hospital (by general practitioners or casualty officers by way of treatment for breast abscesses before incision).—At least 32 of the 37 patients were given one form of antibiotic treatment. Penicillin was most commonly administered (in 13 cases), chloramphenicol in 8, tetracycline in 5, erythromycin in 4, streptomycin in 4, oxytetracycline in 2, and spiramycin in 1. Some patients were treated with various combinations of these drugs.

Interval Between Delivery of Mother and First Incision of Breast Abscess.—Table II shows that few abscesses developed while the mother was still in hospital. 31 (85%) of the abscesses were incised between 15 and 35 days after delivery. One abscess was incised 60 days after delivery. The principles which governed treatment were simple. Nearly all patients had been treated with antibiotics before they were seen by the obstetric staff. The practice of early and adequate

TABLE II.—*Interval in Days Between Delivery and Incision of Abscess*

Days:	0–7	8–14	15–21	22–28	29–35	36–42	>42
No. of abscesses	—	3	8	14	9	2	1

incision and drainage was adopted without waiting for the signs of fluctuation. Some abscesses were multiple and loculated, and a few needed repeated incisions. Huntingford (1958) reports similar difficulties in dealing with breast abscesses caused by staph. phage-type 80 at Perivale Maternity Hospital.

Bacteriology

The organisms responsible for the breast abscesses in this series were all coagulase-positive staphylococci. The strains were as follows:

Staph. aureus penicillin-sensitive, not phage-type 80 ..	6 cases
,, ,, penicillin-resistant, ,, ,, ,, ..	3 cases
,, ,, phage-type 80	27 cases
,, ,, sensitivity unknown	1 case

It became clear that there was an increasing incidence of infection with staph. 80 type organisms *pari passu* with the rising numbers of abscesses occurring in 1957 (see Fig.).

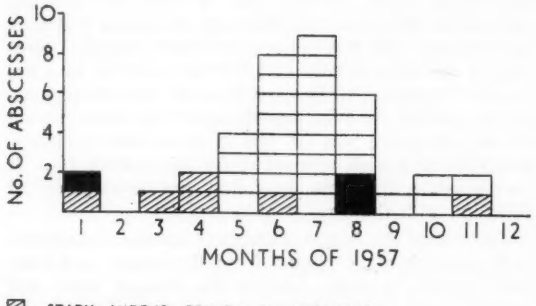

Chart showing increasing incidence of infection with the rising number of abscesses.

Staph. aureus phage-type 80 is an organism which first appeared in this country at some of the larger ports about six years ago, after severe outbreaks in Australasia and North America. It is a virulent strain which produces infection, often in the deeper tissues, giving rise to a protracted clinical course. It is characteristically resistant to penicillin and also to the tetracyclines, but is usually sensitive to chloramphenicol and erythromycin.

Bacteriology of Mothers' Nasal and Vaginal Swabs.—Swabs were taken from the nares and vagina of nearly all mothers on admission to the maternity department. None of the 37 mothers in this series was found to have coagulase-positive staphylococci in the vagina. In only one mother was the organism from a nasal swab of the same type as that grown from her breast abscess. This was a penicillin-sensitive *Staph. aureus*, and a similar organism was grown from a septic spot on the neck of her baby. Thus in only one case was there any correlation between the type of staphylococcus grown from the mother's nares and that isolated subsequently from her breast abscess.

Infants Admitted to the Nursery

Seven babies were admitted for a varying length of time to the nursery, for reasons given elsewhere. The mothers of six of these babies developed breast abscesses of staph. 80 type. 29 babies were not admitted to the nursery, and were nursed in the post-natal wards alongside their mothers. The mothers of 21 of these babies developed breast abscesses of staph. 80 type.

Bacteriology of Mother's Abscess	Baby in Nursery	Baby Not in Nursery
Staph. 80	6	21
Not staph. 80	1	8

These figures are not of sufficient significance to suggest that there was an increase in the likelihood of a mother developing a staph. 80 breast abscess if her child was admitted to the nursery—that is, it was not thought that the nursery acted as a depot for staphylococcal infection.

Babies' Nasal Swabs

Swabs were taken from the babies' noses on delivery and twice weekly afterwards. It was decided not to take throat or umbilical swabs routinely. (Colbeck had frequently isolated staphylococci from nasal swabs when throat swabs taken at the same time were negative.)

In no cases were any pathogens present at birth. The vast majority of babies, however, were carrying staph. 80 in their nares by the fourth to fifth day. Some babies' nasal swabs were persistently negative despite their having pyoderma of staphylococcal origin.

Comparison of the type of organism grown from any one baby's nares with that cultured from his mother's breast abscess shows a striking correlation. This is readily seen in Table III, in which are recorded details of the organisms found in the mother's nose, the baby's nose or other septic focus, and the mother's abscess.

In Case 14 no nasal swab was taken from the baby, but the mother's breast abscess was of staph. 80 type and the baby was subsequently seriously ill with systemic staph. 80 infection (see below).

In Case 15 staph. 80 was not present in the baby's nose, but was isolated from a septic spot on its neck and subsequently from the mother's breast abscess.

In Cases 29 and 30 no nasal swabs were taken because of the laboratory holidays. Both mothers developed breast abscesses from which staph. 80 was cultured.

The total number of babies with *Staph. aureus* phage-type 80 in at least one nasal swab during 1957 was 334.

Neonatal Pyoderma

This includes septic spots caused by staphylococci; umbilical swabs from which staphylococci were cultured are excluded. Of the 14 babies who developed skin infections while they were still in hospital, 12 were shown to be due to staphylococci (all but one were staph. 80 type), including two cases of neonatal suppurative mastitis and one case of staphylococcal ophthalmia.

Sepsis in the Infants after Discharge from Hospital

Any serious illness in the babies in this series would have become known as a result of inquiries made at the post-natal clinics and at the Children's Hospital in the city. Only three cases were discovered—one trivial, one serious, and one fatal.

Case 36.—The baby developed an abscess on the buttock which was incised when the child was 4 weeks old. The mother's breast abscess was incised on the same day. Staph. 80 was grown from both abscesses.

TABLE III

Case No.	Onset of Abscess	Mother's Nasal Swab	Mother's Abscess	Baby's Nasal Swab	Other Septic Foci in Babies
1	January	Negative	Staph. not type 80 (S)	Negative	Nil
2	,,	,,	Staph. not type 80 (R)	,,	,,
3	March	,,	Staph. not type 80 (S)	Staph. not type 80	,,
4	April	,,	,, ,,	Staph. not type 80 (R)	,,
5	,,	,,	,, ,,	Negative	,,
6	May	,,	Staph. type 80	Staph. type 80	,,
7	,,	,,	,, ,,	,, ,,	,,
8	,,	,,	,, ,,	,, ,,	,,
9	,,	,,	,, ,,	,, ,,	,,
10	June	,,	,, ,,	,, ,,	Spots staph. type 80
11	,,	,,	,, ,,	,, ,,	,, ,,
12	,,	,,	,, ,,	Negative	Nil
13	,,	,,	,, ,,	Staph. type 80	,,
14	,,	Staph. not type 80	,, ,,	Not done	Empyema staph. type 80
15	,,	Negative	,, ,,	Staph. not type 80	Spots staph. type 80
16	,,	Staph. not type 80	Staph. not type 80 (S)	Negative	Spots not staph. type 80 (S)
17	,,	Negative	Staph. not type 80	Nil	Nil. Stillborn
18	July	Staph. not type 80	Staph. type 80	Staph. type 80	Nil
19	,,	,, ,,	,, ,,	,, ,,	,,
20	,,	Negative	,, ,,	,, ,,	,,
21	,,	,,	,, ,,	,, ,,	,,
22	,,	,,	,, ,,	,, ,,	,,
23	,,	,,	,, ,,	,, ,,	Eye and breast staph. 80
24	,,	,,	,, ,,	,, ,,	Boil staph. type 80
25	,,	Staph. not type 80	,, ,,	,, ,,	Nil
26	,,	Negative	,, ,,	,, ,,	Spots staph. type 80
27	August	,,	Staph. not type 80 (R)	Staph. not type 80	Nil
28	,,	,,	Staph. type 80	Staph. type 80	Spots staph. type 80
29	,,	Not done	,, ,,	Not done	Nil
30	,,	,, ,,	,, ,,	,, ,,	,,
31	,,	Negative	,, ,,	Staph. type 80	,,
32	,,	Not done	Staph. not type 80 (R)	Not done	Spots staph. type 80
33	September	Negative	Staph. type 80	Staph. type 80	Spots and breast type 80
34	October	,,	,, ,,	,, ,,	Baby died aged 10 weeks of staphylococcal pneumonia
35	,,	,,	,, ,,	,, ,,	Nil
36	November	,,	,, ,,	,, ,,	Spots staph. type 80
37	,,	,,	Staph. not type 80	Negative	Nil

(R) Resistant to penicillin. (S) Sensitive to penicillin.

Case 14.—This child was admitted to the Children's Hospital when 8 weeks old with a history of respiratory infection for three days. He had been breast-fed for two weeks. His mother had then developed a breast abscess from which staph. 80 was isolated. The child was found to have a right-lower-lobe pneumonia and subsequently developed a right-sided empyema from which staph. 80 was cultured. After treatment with tetracycline, erythromycin, streptomycin, and chloramphenicol the child made a slow but complete recovery during 10 weeks in hospital.

Case 34.—The baby was admitted in a moribund condition to the Children's Hospital when 10 weeks old with a history of chest infection for five days. She had been breast-fed for three weeks until her mother developed a breast abscess. The baby died within three hours of admission to hospital. Post-mortem examination showed extensive consolidation of the right lung with abscess formation. The lung was not cultured, but the histologist reported that the lung section showed large clumps of organisms resembling staphylococci. He concluded that the child died from a fulminating staphylococcal pneumonia, as would be compatible with staph. 80 infection.

Staph. 80 was isolated from the mother's abscess which had been incised on two occasions before the baby's illness began. The abscess needed prolonged treatment, and the mother was not discharged from hospital care until five months after the date of her confinement.

Nasal Carriage of Staph. aureus Among Staff of the Maternity Unit

During 1957, 25 members of the nursing staff and four of the domestic staff were found to be nasal carriers of *Staph. aureus* phage-type 80 on one or more occasions. 13 of these had only one positive swab, but one nursing sister had consistently positive swabs for 10 months and one staff midwife for 12 months. Known carriers were excluded from the labour wards, nurseries, and lying-in wards, but some were employed in the isolation ward.

Discussion

Several fortuitous circumstances were favourable to this investigation. The maternity unit had been closed for seven weeks at the end of 1956 to eliminate salmonella infection, and thorough cleansing had been carried out. The low incidence of staphylococcal infection in the early months of 1957 was followed by a rise in later months. At the same time the type of staphylococcus causing the infections changed from a less virulent strain (not phage-type 80, and in most cases penicillin-sensitive) to a high virulent strain (phage-type 80). It was possible, therefore, to follow the development of infection with these resistant organisms.

To control the epidemic staph. 80 carriers among the staff were rigidly excluded from the labour and post-natal wards: patients carrying the virulent strain and those frankly infected by it were promptly isolated. In the later months of the year breast-feeding was discouraged in a number of mothers, but the epidemic had by that time passed its peak, and the value of the introduction of artificial feeding as a means of preventing breast infection could not be assessed fully, though it was probably considerable.

In the epidemic of breast abscesses reviewed in this paper the correlation between colonization of the nares of newborn babies with a virulent strain of staphylococcus and the subsequent infection of the breasts of many of their mothers has been established.

Observations on our patients have shown once more that, whatever else is the cause of persistent staphylococcal infection in maternity wards, the mothers themselves are in no way responsible for the introduction or transmission of virulent strains of staphylococci.

Duncan and Walker (1942) considered that cracked nipples were not essential to the development of breast infection. In this series the presence of a cracked nipple had been recorded in the first week of the puerperium in nine patients who developed breast abscess (24% of the total). The cracked nipple in all cases was on the side which subsequently became infected. The significance of a cracked nipple may possibly lie in the interruption of normal feeding which it causes. Stasis of milk follows with congestion when the breast is not emptied. Attempted manual expression, if done inexpertly, may well aggravate the situation.

The risks of feeding a baby from a breast which is infected have not been taken seriously in some quarters, though Colbeck (1949) and Ravenholt *et al.* (1957) produced striking evidence of the dangers.

In our series one child died from staphylococcal pneumonia and one was seriously ill with an empyema.

When once an outbreak of breast abscess has occurred what measures can be taken to limit its spread? The wards in which the virulent staphylococci are found could be closed temporarily, but with the present demand for maternity beds this policy is not always justified in view of the frequent persistence of infection after such measures have been adopted.

If virulent organisms are grown from the babies' noses attempts could be made to treat this infection with local and systemic antibiotic therapy. However, this treatment would inevitably begin only after contact between a baby's nose and its mother's breast had occurred, unless antibiotics were given prophylactically. The problem of developing resistant strains would then arise.

A third suggestion is that breast-feeding should be stopped, or at least greatly reduced, when virulent staphylococci are abroad in a maternity department. This would appear eminently reasonable, since in a large majority of cases infection of the breast seems to be directly related to suckling and since it has been shown that many mothers stop breast-feeding soon after they are discharged from maternity hospitals.

Summary

An epidemic of 37 cases of staphylococcal breast abscess in the puerperium is described.

Details are given of many particulars concerning pregnancy, labour, and lactation in the mothers affected.

The factors associated with an increase in the incidence of breast abscess are noted, and the relationship is established between organisms isolated from the babies' noses and those subsequently isolated from maternal breast abscesses.

The chronic course of these infections and the danger of serious infection in the infant are stressed.

Possible methods of preventing the spread of such an epidemic are discussed, together with the problem involved in preventing colonization of newborn babies with virulent strains of staphylococci.

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AN OUTBREAK OF DIPHTHERIA

EPIDEMIOLOGICAL ASPECTS

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A dozen years ago, when diphtheria was still prevalent, a small outbreak affecting barely 20 individuals would have merited but passing mention. That such an outbreak occurring to-day can occasion dismay is at once a tribute to the effectiveness of the prophylactic measures introduced during the last war and perpetuated since, and a challenge to any complacency which could lead to relaxation of vigilance. Whenever diphtheria has re-emerged in epidemic form in this country in recent years it has usually erupted with dramatic suddenness, affected a few persons in a small and closed community, and in two or three weeks disappeared almost as rapidly as it began. Nevertheless the consequences can be serious to a minority of those affected.

A local epidemic occurred in Barking, Essex, during September and October, 1958. On the morning of September 30, 1958, the health department was notified by a local isolation hospital that a diagnosis of diphtheria had been arrived at in the cases of two Barking infants' school children. The following details were obtained.

The First Cases

Case 1.—A boy of 7 years, fifth in a family of eight children, was taken ill with a sore throat on return from school on September 19. For four days he was treated at home with antibiotics but did not improve, and on September 24 was admitted to Chadwell Heath (Ilford Isolation) Hospital. Routine nose and throat swabs on admission revealed no pathogens. He appeared to be making satisfactory progress during the next few days, when, on September 29, he developed the signs and symptoms of a toxic myocarditis. The diagnosis of diphtheria was now made on clinical grounds in the absence of laboratory confirmation. This boy died on September 30.

Case 2.—A girl of 6 years, a close friend and class-mate of Case 1, and fourth in a family of seven children, complained of sore throat on September 25. She was seen by a doctor on the 27th, when a diagnosis of tonsillitis was made and antibiotic treatment started. Two days later she was admitted to hospital, where she was found to be gravely ill with membranous pharyngitis, "bull-neck," and cardiac involvement. Diphtheria was diagnosed immediately and antitoxin administered. Throat swabs were examined specifically for *Corynebacterium diphtheriae*, but none were found.

The school class in which these two cases occurred was one of four in a modern single-story infants' school attended by 127 pupils between 5 and 7 years of age. The children, for the most part, kept to their own classes but mixed together during playtime, assembly,

and for certain instruction—for example, singing lessons. Adjoining this school, separated by a wooden fence, are boys' and girls' secondary schools which draw 1,000 pupils from the same area. The infants share the senior school dining-room. Cases 1 and 2 stayed to school dinners.

Immunization State

The class concerned in the infants' school contained 35 pupils born during 1952 and 1953, and record cards held in the health department showed that 17 of them had been immunized, 11 were said never to have been immunized, and no record cards were held for the remaining seven, whose parents could not remember if they had been immunized against diphtheria. No immunization record card could be found for either of the two cases. Of the 127 pupils in the school, 60 were known to have been immunized, 48 had never been immunized, and the position regarding the remaining 19 pupils was in doubt.

On the day of notification teams of doctors and health visitors inspected the throats and took swabs of about 100 contacts of the affected children, including the rest of the class and the patients' families and close contacts. No further suspected cases were revealed by this examination, and, with one exception, all the swabs were negative for *C. diphtheriae*. The exception was a swab taken from an older brother of a boy in the class; this, on the following day, yielded a scanty growth of an organism morphologically resembling *C. diphtheriae* which was subsequently proved to be *C. diphtheriae* gravis.

While we were awaiting the swab results 31 pupils in the affected class were Schick-tested because five or so years had elapsed since some of them had received their primary immunization and the immunity status of others was completely unknown.

Further Cases

Case 3.—On October 4 an unimmunized girl from the same class as Cases 1 and 2 developed a sore throat. She had been under close observation as a contact, and was admitted to hospital on the same day without previous treatment at home. Antitoxin was given at once and she was never seriously ill. Virulent *C. diphtheriae* gravis was subsequently grown from the nose and throat swabs taken on admission, but it is of interest to note that she had been among those swabbed with negative results three days previously.

Case 4.—The next day another 6-year-old girl from the class was found, on a routine visit, to be suffering from sore throat with slight exudate on both tonsils. She was admitted to hospital, where she was given antitoxin and the diagnosis of diphtheria was confirmed bacteriologically. She suffered a mild attack only. This patient had received a single dose of combined diphtheria toxoid and pertussis vaccine over five years before.

As a result of these developments it was decided to close temporarily the affected class and to administer prophylactic serum to its nine remaining Schick-positive members. In addition, it was decided to re-swab the affected class and home contacts and to Schick-test and swab the pupils in the other three classes of this school. The school staff was also included in the investigations.

Case 5.—On October 7 diphtheria was diagnosed (and subsequently confirmed bacteriologically) in a girl of 12 years who had never been immunized. She had been ill for four days before she was seen, admitted, and given antitoxin, and had a severe attack from which she eventually made a good recovery.

Case 6.—A brother of Case 5, aged 6, was a classmate of the four known cases. This boy had already been swabbed twice, with negative results, yet a repeat swab taken on October 7 was positive; but though he was never immunized (according to available records), the disease was aborted at an early stage, probably because two days previously, when his Schick test was found to be positive, he had been given prophylactic serum. His sister had last been at school on September 29, but, fortunately, no cases or carriers were revealed among her class-mates on routine inspection and swabbing.

Detection of Carriers

Further carriers were now being detected, among them the original doubtful positive found during the first mass swabbing and three more members of his family, including his mother, whose swabs had previously been negative. The second sweep through the affected class revealed two carriers among the pupils, one of whom had received prophylactic serum a few days earlier on being found to be Schick-positive.

Hospital treatment was arranged for the carriers at first, but as the demand for beds for cases and carriers grew this tended to overwhelm the available accommodation, and it was decided, with the co-operation of the family doctors, to isolate and treat healthy carriers in their own homes if conditions permitted.

Despite their fairly close contact with the pupils in the affected class, swabbing of the pupils in the three unaffected classes did not bring to light any more carriers. Schick-testing revealed that 28 pupils in the remaining classes were susceptible, and it was decided to protect these children by simultaneous administration of antitoxin and antigen, a procedure suggested by Downie *et al.* (1948). A.P.T. was chosen, despite the slight risk of provoking poliomyelitis (M.R.C., 1956), because at the time the district was free of this disease and it was thought that a potent antigen such as A.P.T. is more likely to lead to a satisfactory level of immunity in the presence of small amounts of antitoxin. This combination of serum and A.P.T. was used for the close contacts. Others were given T.A.F. or F.T., and approximately 1,800 children were immunized or received a booster dose of antigen within a few weeks of the epidemic which stimulated a marked increase in the demand for diphtheria immunization.

Cases 7 and 8.—Throat swabs taken from two older brothers of one of the carriers in the class were found to be positive on October 8. When seen at home both boys had slightly sore throats with scanty exudate. They were admitted to hospital, treated with antitoxin, and notified as cases of diphtheria. Both boys had been immunized some years previously, and in each case, despite the virulence of the organism, the illness was mild.

Case 9.—The only patient not of school age was now detected. A boy of 2 years was admitted to hospital on October 9 with inflamed tonsils sparsely covered with exudate. The diagnosis was later confirmed bacteriologically. He was bright and active and was never very ill. His sister attended one of the unaffected classes of the primary school. He lived in the area in which most of the cases and carriers were found. This boy's father, a labourer, and the sister already mentioned, were subsequently found to be carriers and treated at home.

Case 10.—On October 10 a sister of Case 5, aged 8 years, developed a sore throat and was sent to hospital as a suspected case of diphtheria. Bacteriological confirmation was later obtained. She had not been immunized, and though detected at an early stage, through being under close observation as a contact, she had quite a severe attack.

Case 11.—This boy, though at first thought to be a carrier, was sent to hospital and presented a diagnostic problem to the clinicians, who eventually notified him as a case of mild faucial diphtheria. He was one of the members of the affected class who had never been immunized, and was found on October 3 to be Schick-positive. Two days later he was given prophylactic serum. A repeat swab taken on October 7 was found to be positive (he had previously been swabbed, with negative results), and he was admitted. His condition was satisfactory throughout. His uncle, a bus conductor, who lived in the same house, was found to be a carrier and was successfully treated at home before resuming his employment.

Case 12.—The source of the infection introduced to this class before September 19 had not been discovered, and things were settling back to normal when an interesting development occurred. A boy aged 7 years from the affected class, where he sat next but one to Case 1, had attended school from September 8 (the day of reopening after the summer holidays) until the 12th, when, soon after returning from school, he began to complain of sore throat and difficulty in swallowing; then his neck gradually became swollen. A locum doctor who saw the boy on the 15th was said to have stated that the boy was suffering from mumps and a "coccal" throat. But the entry made by the same doctor on the boy's medical record card on September 24 read: "Very severe streptococcal throat infection with oedema. Made very satisfactory recovery with penicillin, M. & B., achromycin (not all at once)." There was nothing to indicate that this diagnosis rested on any bacteriological evidence, as no swab seemed to have been taken.

When these facts came to light during our epidemiological inquiries the boy was medically examined and swabbed several times, but, though he was observed to be rather listless and lethargic, the only definite abnormal finding was an E.C.G. tracing which showed an occasional ventricular extrasystole. But on October 22, about six weeks after his illness, from which he had apparently made a full recovery, the boy returned to his family doctor with bilateral palatal paralysis. He was admitted to hospital and notified as a faucial (missed) case of diphtheria. He made a very satisfactory recovery in a few weeks. Further investigation did not reveal the source of this boy's infection.

In addition to the 12 cases described, 14 carriers were detected. Of these 26 individuals, 23 were members of the affected class, had a sibling in the class, or were very closely associated with a known case or carrier. Three adult carriers were detected, and only one of the patients was under school age. Pupils of six different schools were included in the 22 schoolchildren involved. Routine swabbing was carried out on all pupils at the infants' school and on the 1,000 pupils of the adjoining senior schools. Pupils attending five classes in four schools who might have been contacts of cases or carriers were also swabbed. Bacteriological investigation of the mass swabbings was carried out at the Public Health Laboratory, London County Hall, and out of approximately 3,000 swabs submitted only one carrier was discovered who could not be regarded as closely associated with any of the known cases or carriers. This small number found in what might be regarded as the general community of schoolchildren supports the supposition that it is rare nowadays to find carriers except among persons closely associated with an outbreak.

The remaining 22 individuals with positive swabs were first detected by our own examination of upwards of 1,000 swabs submitted from the patients and their close contacts in the school or home communities. The bacteriological investigation is described elsewhere (Kehr *et al.*, 1960). Through the kindness of the director, Dr. A. J. H. Tomlinson, 21 of these 22 strains were also sent to the County Hall Public Health Laboratory for confirmation and guinea-pig virulence tests. All were found to be virulent *C. diphtheriae* gravis.

In all, some 4,000 swabs from 1,800 persons were submitted for examination and a vast amount of work was carried out by medical, nursing, and administrative staffs in following up contacts and keeping them under observation.

Previous Immunization History

One of the patients (Case 7), aged 13, had a full course of immunization in 1946, with a booster dose in 1950, and his brother (Case 8), aged 10, completed his primary immunization in 1950 and had a booster injection in 1954. Two other children had begun a course of primary immunization five and seven years previously but had not completed it. No immunization record cards could be found for the remaining eight cases, including the original two cases. Nine of the carriers, including two sisters of Cases 7 and 8, had been immunized at some time. Three others, carriers who had never been immunized, had been protected by prophylactic serum. Three adult carriers were detected.

Protective Methods

When the fourth case developed in the affected class nine pupils in the same class, found to be Schick-positive, were given 8,000 units of antitoxin each in order to prevent further spread among the exposed unprotected children; 0.5 ml. of A.P.T. was given two weeks later to this group, and this was repeated after a further six weeks. Only five of these children were post-tested three months later and each was found to be Schick-negative.

In the remaining classes of the affected school 28 pupils received simultaneously 500 units of antitoxin in one arm and 0.5 ml. of A.P.T. in the other. Six weeks later each received a repeat dose of A.P.T. Post-testing of 22 members of this group after an interval of three months showed that all had been converted to Schick negative.

Anaphylactic Reactions.—Antitoxin treatment was followed in two cases by fleeting urticarial eruptions. There were no other sequelae.

Treatment of Carriers

Eight carriers were treated at home and the remainder in hospital. The sensitivity pattern of the infecting strain in each case was ascertained before starting treatment. In all cases the organisms were found sensitive to penicillin, erythromycin, tetracycline, novobiocin, and sulphafurazole (which was the representative sulphonamide used). Four patients were given orally tablets combining 120 mg. of penicillin and 0.88 g. of sulphonamide four-hourly for four days. On reswabbing three days after completion of this, two of the four were found to be still positive. They

subsequently responded to erythromycin in doses of 200 mg. six-hourly for four days. Erythromycin in the same doses was successful as the initial treatment of another carrier, a brawny labourer.

Three children were initially treated with oral penicillin alone (125 mg. of penicillin V six-hourly for four days); two did not respond. One of these responded to a subsequent course of erythromycin. The other was also given a course of erythromycin and finally 250 mg. of oxytetracycline six-hourly for four days, but his throat swab remained obstinately positive. He was eventually seen by a consultant ear, nose, and throat surgeon, who enucleated his tonsils and adenoids, not merely because he was a persistent carrier, but because the unhealthy state of his pharynx justified the operation, which, in the event, effectively cured the carrier condition.

Discussion

Bloss (1955) observed: "The type of the organism is common to the outbreak, the cases occurring in small family circles or in localized residential areas. The source of the original infection is usually difficult and often impossible to find. . . . Diagnosis was frequently delayed, particularly in atypical cases."

Our experiences during this outbreak provided abundant corroboration of these statements. Not the least of our problems was the difficulty of clinching the bacteriological diagnosis at the beginning. Though fully alerted to the possibility of diphtheria from September 30 onwards, it was not until October 2, after screening nearly 200 swabs, that we encountered the first swab that we could regard as doubtfully positive. The child from whom this swab had been taken, an older brother of a boy in the affected class, was not clinically ill, and only scanty organisms exhibiting the morphology of corynebacteria were obtained among a profuse growth of other throat commensals. Cultures had to be carefully husbanded for further tests, and three or four days had elapsed before we had unequivocal proof from fermentation reactions that the organism was *C. diphtheriae* gravis.

Our difficulties were finally resolved when, on October 4, Case 3 was admitted, untreated and non-immunized, with a sore throat. Throat swab cultures from this girl quickly yielded colonies that could be confidently identified as *C. diphtheriae*, probably gravis.

It is almost a truism that "the diagnosis of diphtheria is the responsibility of the clinician" (Mackie and McCartney, 1953), and, in a disease the treatment of which depends so much for its effectiveness on the early administration of antitoxin, this cannot be too often stressed, but bacteriological confirmation of the diagnosis is none the less important. To no one perhaps is this more vital than it is to the medical officer of health. He has to decide whether to issue to general practitioners a warning, the effect of which may well overwhelm the resources of local isolation hospitals, whether to take action which may interfere with the normal educational or vocational pursuits of individual citizens, how wide to cast the net of his mass swabbing campaign, etc. Conscious of the fickleness of public opinion and the scrutiny of an ever-watchful press, he must strike a delicate balance between the twin evils of failing to take proper safeguards and "crying 'Wolf'" For succour in all this he has a right and a duty to appeal to the laboratory.

But out of 159 cases for which details are available of the 166 corrected notifications in England and Wales in 1954, 28 were diagnosed on clinical grounds only and *C. diphtheriae* was not isolated, and in one other case the diagnosis was made clinically without a swab being taken (Bloss, 1955). In this outbreak, from the morning that the local health department first became aware of the possibility of the disease two whole days had elapsed before laboratory investigation led to the first hint of a positive finding and three more days before a categorical affirmative was forthcoming. Bloss concluded that "the readily dispensed treatment of tonsillitis with sulphonamides and antibiotics, though it was doubtless of value to the patient [*sic*] complicated the bacteriological investigations." It certainly seems that the prior exhibition of antibiotics in our Cases 1 and 2 vitiated the laboratory investigations.

Another point touched upon by Bloss is "the doubt in some cases as to whether a positive bacteriological finding indicated a case or a carrier." We were similarly perplexed with some of our cases—for example, Cases 6 and 11. It is obviously undesirable to rush people needlessly into hospital, and, where there is unequivocal proof of a person's immunity—that is, reliable records of recent immunization and/or a negative Schick reaction—coupled with an assurance of fitness, based on careful clinical assessment, such an individual, even though bacteriologically positive, may be kept under surveillance at home. But where doubt exists we feel that, on balance, it is wiser to regard such individuals as "cases," however mild, rather than carriers. Their number would very likely be so small that available isolation facilities could be expected to be adequate. In any case, bacteriologically positive persons must be segregated somewhere, at least until those in charge have got the measure of the epidemic.

Though the original source from which the infection was introduced to this school class was never detected, it seems likely that Case 12 was the first child to develop the disease. There can be no doubt, in view of his sore throat, the vague story of concurrent mumps (? missed "bull-neck"), his poor general condition during the ensuing weeks of observation and the late palatal palsy, that he had diphtheria on or about September 12. It is true that he ceased attending school on that date, and the interval of seven days until Case 1 became ill would postulate a rather long incubation period, but only if opportunity for infection were restricted to contact at school. There are two other possibilities: (1) case-to-case contact at home some time between September 12 and 19 cannot be discounted, and (2) indirect contact through a healthy transient carrier: our mass swabbing and reswabbing amply demonstrated the transitory nature of the presence of the organism in the throats of many of these children.

The evidence, therefore, unmistakably points to Case 12 as the original case in this school community. Diphtheria has become so rare a disease in this country in recent years that few doctors in their first decade of practice have seen it at all, and older practitioners have to rely on long memories when trying to diagnose a possible sporadic case. That the diagnosis should

remain unsuspected in such a case is thus perfectly understandable and reflects no discredit on the clinical acumen of any physician. But we do feel that it was a pity that, in the absence of any attempt at bacteriological confirmation, Case 12 was written off as "streptococcal tonsillitis." This diagnosis made—as, in our experience, it not infrequently is—with the unaided senses is not merely a delusion of muddled minds, it is a dangerous snare which by the mesmeric influence of a jargonistic label closes the mind to the possibility of reappraisal. "Tonsillitis" is a perfectly valid clinical diagnosis; only the laboratory can ascribe to it a specific aetiology.

We do not wish to embark here on the perennial controversy concerning the indications for antibiotics or chemotherapeutic agents in the treatment of acute sore throats, but it is pertinent to plead that if the physician in charge has made up his mind to administer one of these drugs he should at least take a throat swab—he need not await the result of the culture—before starting his course of treatment.

Summary

A localized epidemic of diphtheria involving 12 cases (one fatal), the brunt of which fell on one infants' school class, is described. Virulent *C. diphtheriae* gravis was isolated from nine of these cases and 14 other carriers. The relatively low immunity status of the school community (less than 50% of the children having been immunized) was thought to be an important factor in the development of the epidemic.

The treatment of carriers is considered, the obstacles (notably the widespread use of antibiotics) to bacteriological diagnosis are recounted, and the difficulties in tracing the original source of infection is discussed.

Our thanks are due to Dr. A. J. H. Tomlinson and the staff of the Public Health Laboratory, London County Hall, for accepting our strains for confirmation and virulence tests, and for accepting direct the enormous number of swabs taken when the mass swabbing had to be extended. It is a pleasure to acknowledge our debt to the medical, nursing, and administrative staffs of the Barking Public Health Department and to local family doctors for their ready help and full co-operation throughout the epidemic.

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The *British and Overseas Pharmacist's Year Book 1960* has now been issued by the publishers, the British and Colonial Druggist Ltd., organizers of the National Pharmacy Exhibition and the London Medical Exhibition. Though primarily for the pharmacist, the *Year Book* contains much information that would be of interest to the general practitioner, including sections on the Pharmacy and Poisons Act, the Dangerous Drugs Act, and on the National Health Service (112+xvii pp.; price 5s.).

TREATMENT OF THE CARPAL-TUNNEL SYNDROME*

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The carpal-tunnel syndrome consists of paroxysmal paraesthesiae, pain, and subjective numbness in one or both hands, often accompanied by some objective impairment of sensation in the digits supplied by the median nerve, and by muscular weakness and wasting in the thenar eminence. It affects women predominantly, and untreated it usually pursues a variable course, with exacerbations and remissions, for years. Paroxysms occur most commonly in the night and are often of such frequency and severity that the sufferer can get little sleep for weeks on end. By day, symptoms may be induced by use of the hands, and many patients have to give up much of their ordinary domestic occupations. Thus this syndrome can be a source of great distress and disability to those affected by it.

It is a common condition. Brain *et al.* (1947) described six cases of the fully developed syndrome. By their work the carpal-tunnel syndrome was established as a definite entity, caused by compression of the median nerve within the carpal tunnel, and capable of being relieved by division of the flexor retinaculum. In the ensuing years there have been a number of reports of much larger series (Kremer *et al.*, 1953; Garland *et al.*, 1957; Heathfield, 1957) which reveal that the diagnosis is being made with increasing frequency and the diagnostic criteria are becoming less rigid. It has been shown that patients with "acroparaesthesiae," who even after years of persistent symptoms may have no objective physical signs, are suffering from the carpal-tunnel syndrome and can be relieved by this simple surgical procedure. A diagnosis of the carpal-tunnel syndrome is now a commonplace in general medical, neurological, and orthopaedic practice.

The main standby of treatment is operative decompression of the median nerve in the carpal tunnel by division of the flexor retinaculum. Before the work of Brain *et al.* (1947) the successful use of this operation was reported by Woltman (1941), Zachary (1945), and Cannon and Love (1946). Its effectiveness has been well attested in a number of large series since then. Brain and Strauss (1955) and Garland *et al.* (1957) regard it as being the only effective treatment.

Immobilization of the wrist has, however, been shown to be effective in relieving symptoms. It was first recommended by Roaf (1947) as both a diagnostic and a therapeutic measure. Phalen and Kendrick (1957) found it successful in mild cases of short duration. Heathfield (1957), who also used immobilization as a diagnostic measure, reported symptomatic relief in 48 out of 51 cases. He immobilized the wrist in the neutral position by means of a splint which was worn at night and in some cases also by day. Relief of symptoms occurred rapidly, and after wearing the splint regularly for from six weeks to three months 34 of the 51 cases remained free from recurrences during a follow-up period of from 6 to 30 months.

Another method of treatment that has been reported to be successful is injection of hydrocortisone into the

*This communication is based partly on an investigation which was the subject of a thesis for the degree of M.D., Aberdeen.

carpal tunnel. Phalen and Kendrick (1957) treated 20 cases in this way, and claimed remission of symptoms in 16, only one injection being required in some. Kopell (1958), Richmond (1958), and van der Bracht (1958) have also reported similar successful results, the latter combining a relatively large volume of local anaesthetic with the hydrocortisone injected. Meanock (1958), too, found this method of value in cases of recent onset.

The object of this communication is to report on the use of these three methods of treatment.

Material

The present series consists of 81 cases of the carpal-tunnel syndrome (72 female and 9 male). 50% of these patients were between the ages of 40 and 59 when the diagnosis was made, but when the age of onset is considered the incidence in each decade from the third to the eighth is respectively 13, 17, 17, 18, 13, and 3. The duration of symptoms before diagnosis varied from a few weeks to 44 years, being less than one year in 27 and over 10 years in 13. Symptoms were bilateral in 51 and unilateral in 30.

The syndrome was associated with carpal osteoarthritis in four patients, with rheumatoid arthritis in seven, with primary generalized osteoarthritis in 12, and with acromegaly in two. In 16 patients the onset occurred during pregnancy or early in the puerperium. The onset was clearly related to a specific incident or a period of strenuous use of the hands, or to occupational factors, in 23 patients, and there was a less definite but probable relation to work in another 12.

Before the correct diagnosis was made a great variety of oral and parenteral drugs had been given to these patients, often over long periods, with invariable lack of success. Local therapy to the hands in the form of ointments, massage, heat, wax baths, and electrotherapy had proved ineffective. Six patients had received physiotherapy to their neck and shoulders, and several had had their cervical spine manipulated, all without definite benefit.

A few patients had at some time obeyed their doctors' instructions to have a complete rest from work and had been temporarily relieved. One who was made to wear the affected arm in a sling for two months had a complete remission lasting 12 years.

All of the patients have been followed up for at least one year after completion of treatment, apart from a few of those treated surgically who were kept under observation for only a few months after operation.

For purposes of description they can be divided into four groups: those who received no specific treatment, those treated initially by immobilization, those treated with local hydrocortisone, and those treated surgically, either initially or after failure of other methods.

No Treatment

Nineteen patients received no active treatment. Two refused treatment and were still suffering from symptoms of varying severity two or more years later. Three patients whose symptoms were not severe were satisfied when reassured of their benign nature. One acromegalic received radiotherapy to the pituitary gland, which brought about improvement in his acromegalic state and was followed by remission of the syndrome.

In 13 patients symptoms remitted spontaneously and did not recur, except for brief episodes of mild paraesthesiae in a few, during a follow-up period of one to five years. This remission followed the conclusion of pregnancy in three and a reduction in manual work in four, while in four others it occurred, after as long as six years, for no discoverable reason. In two patients the syndrome was of sudden onset after a specific incident of manual work, and spontaneous recovery occurred after some months.

In several of these patients the marked sensory loss and wasting that were present at the time of diagnosis recovered completely. This was most striking in the last two referred to.

Immobilization

Immobilization was achieved by means of a close-fitting anterior splint, made of plaster-of-Paris, which extended from the upper part of the forearm to the metacarpophalangeal joints. This was worn by the patient at night, being kept in position by light bandaging, and held the wrist immobilized in a *neutral* position. Thirty-six patients were treated in this way, of whom 18 received splints to both wrists. The duration of their symptoms varied from a few weeks to 19 years, and all degrees of severity of symptoms and of motor and sensory loss were represented.

Nineteen of these patients received immediate relief of nocturnal symptoms, and this was followed by a slower subsidence of diurnal symptoms. One of these, however, had a severe relapse after six weeks, though she continued to wear the splints regularly. In another eight patients benefit was not apparent for one or two weeks, and complete freedom from nocturnal paroxysms did not occur in some for several months. In a few of this group the wearing of splints seemed at first to exacerbate the condition, but after a few nights benefit was felt and thereafter nocturnal symptoms subsided completely. Nine patients were not benefited in any way, and a few of these claimed that the splints so increased their symptoms that they were unable to continue wearing them.

The patients who improved with this treatment wore their splints regularly at night for periods varying from three weeks to six months. Many who discarded them after a few weeks suffered an immediate relapse and had to continue using splints for a longer period. All of them were able to discard the splints eventually without an immediate return of symptoms, but several had later recurrences which did not always respond to resumption of the splints.

Only five can be said to have been "cured," and the longest period of follow-up observation in these is two years. One of these developed the syndrome in pregnancy and wore the splint regularly until after delivery. Another was an acromegalic whose acromegaly appeared stationary and who remained symptom-free after wearing the splint for six months. Ten others are very satisfied with the results of treatment, but still suffer from mild recurrences, usually precipitated by work, which necessitates their resuming the use of splints for a few successive nights. Of these, two had carpal osteoarthritis and one had rheumatoid arthritis.

Neither the duration of symptoms before treatment nor the presence or absence of signs of neuropathy seemed to have any bearing on the response to splinting. A close analysis of the data of these cases fails to reveal any common factor by which the response of any individual case might be predicted. In some cases with

bilateral symptoms, one side would respond well, while the other would not. The results in such cases are classed according to the more unfavourable response.

In 21 patients treatment by immobilization can be regarded as having failed: three continue to have troublesome symptoms which are only partially relieved by intermittent use of splints; 13 were subsequently treated with local hydrocortisone; and five received surgical treatment.

Local Hydrocortisone

Twenty-two patients, including 13 in whom immobilization had failed, were treated by injection of hydrocortisone into the carpal tunnel. The technique of injection was as follows. The wrist is first examined to identify, if possible, the median nerve and also to ensure that neither of the main arteries runs an abnormal course across the flexor aspect. Then, with the wrist and fingers in flexion against resistance, the tendons of flexor carpi radialis and of palmaris longus (if present) are identified. After preparation of the skin and the production of local anaesthesia, with the wrist relaxed in a position of about 45 degrees extension, the needle is inserted at the proximal skin crease at the wrist immediately on the ulnar side of the tendon of flexor carpi radialis, making an angle of about 60 degrees with the forearm. It is then advanced deep into the carpal tunnel between the tendons of the finger flexors. In some cases the structures within the tunnel appear to be tightly compressed, but, by gently moving the point of the needle from side to side as it is advanced, a path between the tendons is readily found. The injection is performed during withdrawal of the needle, which is moved up and down and from side to side between the tendons so as to distribute the hydrocortisone fairly uniformly throughout the tunnel.

In some of the early cases treated in this way, 4 ml. of local anaesthetic was injected into the tunnel before or along with the hydrocortisone, but this appeared to cause a painful sensation of swelling and stiffness of the wrist and fingers which persisted for as long as 48 hours. In later cases no local anaesthetic (apart from an initial small subcutaneous injection) was used, and the procedure seemed to cause less pain at the time and less discomfort afterwards. Usually 50 mg. of hydrocortisone acetate was injected, but in many cases 37.5 or 25 mg. only was given, and the results did not appear to be any less satisfactory.

In these 22 patients 31 hands were treated, and the results in 28 were dramatic. After an initial period of 24 to 48 hours of discomfort or pain and stiffness, patients found that their symptoms had abated to a great extent or had entirely gone. In 10 instances the injection was repeated after one or two weeks, as the relief, though immediate, had not been complete, and in each case this completed the "cure." All patients were encouraged to continue working with their hands in the normal way, and even to try doing things that before treatment would have been sure to give them trouble. They were all surprised and delighted to find that they could now do their gardening or spring-cleaning, or knit or sew, without provoking symptoms.

One patient who had bilateral symptoms of 20 months' duration received only partial relief. No improvement whatever occurred in another patient with unilateral symptoms of 11 years' duration. The latter had previously failed to respond to splinting of her wrist, but was later completely relieved by operation.

The ages of those who responded, of whom two were male, varied from 29 to 70 years, and the duration of symptoms from two weeks to 19 years. None of these patients was suffering from rheumatoid arthritis. One had carpal osteoarthritis, and one was treated two weeks after the onset in the fourth month of pregnancy. Symptoms were severe in all of these patients, and physical signs of neuropathy were present in all but one whose symptoms were of only six weeks' duration.

The later results of local hydrocortisone therapy, however, did not bear out its initial promise. Symptoms recurred in 16 of the 20 "successes" within one to eight months. Nine were then given a second course of injections consisting of two or three weekly injections of 25 to 50 mg. Seven of these again had a complete cessation of symptoms only to relapse within four months. One failed to improve a second time, though given three injections of 50 mg. One was partially relieved, and had no recurrence of severe symptoms in the year she remained under supervision. Two patients received a third course of injections with complete success but relapsed respectively three and six months later.

In only two cases can this form of therapy be regarded as completely successful, but the result was satisfactory in a third. One was the patient already referred to whose symptoms began in the fourth month of pregnancy. She was completely relieved by one injection and had no recurrence during a 14-month follow-up. The second was a 75-year-old woman with bilateral carpal osteoarthritis and bilateral symptoms. Immobilization had been completely successful in one hand, but failed in the other. After two injections in the latter she had no further symptoms during a 14-month follow-up. The third, whose symptoms were of only six weeks' duration, suffered from occasional minor paraesthesiae throughout the ensuing year. One other patient who had responded fully to injection received surgical treatment as she chose not to risk the possibility of relapse.

Of these 16 failures, eight later received surgical treatment, which was successful in all, and one is awaiting operation. The remaining seven patients still have symptoms of varying severity, though some express themselves as pleased with the result of treatment. Several have reverted to the use of splints.

In this series of 65 injections, infection was introduced into the flexor tendon sheaths on one occasion. This occurred early in the series and was due to faulty technique. When a reasonable standard of asepsis was observed (the aim being to take the same precautions as are usually observed in the performance of a lumbar puncture) there were no complications. The patient who developed synovial infection was treated early with tetracycline, followed by physiotherapy, and made a complete recovery with no residual disability.

Surgical Treatment

Thirty-one patients had surgical treatment, of whom seven had previously been treated with hydrocortisone or immobilization, and seven had received both. Nine of these had operations on both sides, and two had two operations on the same side. These 42 operations were performed by several different surgeons and the method of operation was not the same in all cases, but the essential object in each case was the complete division

of the flexor retinaculum. In some cases a transverse incision at the wrist was used and the retinaculum divided "blindly." In others it was displayed through a longitudinal incision extending into the palm and divided under direct vision.

Of the 40 median nerves exposed at operation, only 11 showed any abnormality. In these there was obvious constriction of the nerve within the tunnel and swelling of the nerve immediately proximal to it. In some cases there was a distinct transverse groove on the nerve at the level of the proximal edge of the flexor retinaculum. The finding of such obvious changes bore no relation to the duration or severity of the symptoms or signs. In two cases (one of which had had local hydrocortisone) fine adhesions were found surrounding the nerve. In some cases the cut edges of the retinaculum separated widely immediately after division, demonstrating the presence of increased tension within the tunnel. In one case the retinaculum was thought to be abnormally dense and in another the flexor synovial sheaths were thickened and oedematous.

The results of 35 operations were excellent. Patients almost invariably experienced immediate relief from severe symptoms and most of them within a few weeks were free from all symptoms. In a few, minor episodes of paraesthesiae continued to occur intermittently but were never severe enough to cause any inconvenience. Objective sensory impairment and muscular wasting improved slowly after operation in most cases and in a few made a full return to normal, but where they were severe before operation, even if of short duration, complete recovery never occurred. However, all of these patients expressed themselves entirely satisfied with the results of operation, and even those who had residual gross wasting and very definite sensory impairment were aware of little or no disability. In four patients with bilateral symptoms successful operation on the more severely affected side was followed by rapid subsidence of symptoms in the other hand.

The results of operation in three patients were not so immediately satisfactory. In one patient, who had a considerable post-operative haemorrhage into the carpal tunnel, symptoms persisted, though with greatly diminished frequency and severity, and they were still present two and a half years later. The second patient, who had both flexor retinacula divided in pregnancy, and in whom one nerve was observed to be constricted, improved, but her symptoms did not cease completely until after delivery. The third patient, who had very severe symptoms before operation, was entirely relieved of pain but continued to have troublesome paraesthesiae. The period of post-operative observation in this case was, however, only two months.

Two patients each had two operations on the same wrist. One, whose symptoms were completely relieved after operation, had a recurrence one month later. Permanent relief followed the second operation, at which it was found that the distal part of the retinaculum had not been divided. A second operation was performed in the other case for the same reason. Symptoms were relieved, but the median nerve at the wrist was damaged and permanent sensory impairment resulted.

Post-operative complications developed in two patients. The first suffered a relapse after two months and developed a "trigger wrist" associated with a cystic swelling arising from the flexor sheaths at the wrist. A similar sequel to operation has been described by Kremer *et al.* (1953), and their patient was relieved once more by the removal of such a cyst. This patient's symptoms subsided almost completely without operation. In the second patient the wound burst when the stitches were removed and she suffered a severe recurrence of symptoms, which, however, subsided spontaneously.

Discussion

Methods of treatment other than those described here have been advocated. Kendall (1950), who regarded external pressure on the palm as an important aetiological factor in younger patients with unilateral symptoms, was able to relieve several patients whose occupations involved such pressure by providing them with a pad to protect the palm. It is difficult to reconcile this result with current views on the aetiology of the syndrome; in any case, such treatment would be applicable to very few sufferers indeed.

The administration of oestrogens has been reported to be effective by a number of authors. Young (1950), Schiller and Kolb (1954), and Reid (1956) claimed relief of symptoms, sometimes permanent, in menopausal patients after intermittent or continuous administration for several months. In the large doses used, a number of their patients had abnormal uterine bleeding or toxic symptoms. Layton (1958) used stilboestrol (in doses of 150 mg. daily) in pregnant sufferers with success. On the other hand, Kremer *et al.* (1953) found oestrogens to be entirely ineffective. When the difficulties and troublesome effects of continued administration of oestrogens are taken into account the reported success of such treatment is not consistent enough to recommend its routine use.

Diuretics, with or without fluid and salt restriction, have been used with success in a few isolated cases, especially in pregnancy (Jones, 1953; Guly, 1959; McCallum, 1959; Wood, 1959). The danger of electrolyte depletion makes long-term therapy of this nature undesirable, but it merits further investigation.

Exercises and other forms of physiotherapy aimed at elevating the shoulder girdles have in the past been said to relieve the symptoms of the carpal-tunnel syndrome, and this belief is still expressed (*British Medical Journal*, 1959). No evidence of lasting relief has been published. Walshe (1945) found such treatment of no value unless preceded and accompanied by a long period of complete rest from manual work. Turner *et al.* (1958) found it helpful sometimes but of limited value. Six patients in the present series had had prolonged courses of physiotherapy to their shoulders and none had received any definite benefit. In two of these cases the hospital notes of the time were available, and in them symptomatic improvement was recorded after weeks of treatment, but the patients later denied having received any memorable or lasting relief.

As in other disorders that are subject to spontaneous remissions, the results of any form of therapy for this syndrome must be viewed critically, and success can be claimed only after an adequate period of follow-up supervision. Seventy cases in the present series were the subject of a detailed investigation, and it was found that 59% of them had experienced complete spontaneous remission of symptoms for periods varying from a few weeks to a few years. Such remissions were initiated in some cases by a period of complete rest, or a change of

occupation, or a reduction in manual work, or a spell of warm weather, but in others they occurred for no discoverable reason. Prolonged remissions occurred without any treatment after symptoms had been continuously present for as long as six years.

This investigation also revealed that many of these patients, when their complaint was diagnosed and some explanation of their symptoms given, would for the first time, and quite spontaneously, take steps to reduce their manual work. (It was for this reason that all patients in this series receiving hydrocortisone were specifically instructed to carry on with their full normal occupations.) In some cases this alone may initiate remission, and the credit may be given to whatever therapy has been applied. This consideration does not apply to cases treated by operation or local hydrocortisone, nor to most of those treated by immobilization, for in all of these improvement is almost immediately apparent. It does apply, however, to those in this series who received delayed benefit from splints, and it certainly also applies to the claims that have been made for shoulder-girdle therapy.

Conclusions

Both immobilization of the wrist (Roaf, 1947; Heathfield, 1957) and local hydrocortisone (Crisp, 1959) have been recommended as diagnostic procedures for cases where the diagnosis is in doubt. In this respect local hydrocortisone is greatly to be preferred. It is far more reliable, since only 1 out of 22 patients failed to receive definite benefit from one injection, whereas immobilization had no effect in 9 out of 36 patients. Furthermore, it is easier and quicker to apply and the results are apparent within one or two days.

The choice of the method of treatment in any particular case must be influenced by many factors. The age, occupation, and state of general health of the patient, the circumstances of the onset, the severity of the symptoms, the severity and rate of progression of wasting and sensory loss, the presence of associated diseases such as rheumatoid arthritis, acromegaly, or myxoedema, and, of course, the patient's preference, have all to be taken into account. It is impossible to make any definite recommendation that will be applicable to all cases, but from the present study some conclusions can be drawn.

Injection of hydrocortisone into the carpal tunnel will in almost all cases bring about a striking remission of symptoms. It is therefore worth using to bring immediate relief in severe cases, whatever other treatment is proposed. In patients who develop the syndrome in pregnancy or after a specific incident or period of manual work—that is, in those most likely to recover spontaneously—it can be expected to give lasting relief. In patients with carpal or generalized osteoarthritis, in whom compression in the carpal tunnel may arise from a secondary tenosynovitis, it may have a lasting effect. It is worth a trial in patients who can change a harmful occupation or reduce their manual work. A trial is justified, too, in patients with rheumatoid arthritis. In most cases, however, local hydrocortisone, as used here, causes only a temporary, though sometimes lengthy, remission.

Immobilization of the wrist at night induces a fairly rapid remission in about 75% of patients, but the long-term results are likely to be satisfactory in only about half of these. Though some authors (Lang, 1954; Phalen and Kendrick, 1957) have recommended immobilization only in cases of recent onset, the experience in this series indicates that cases of even very long duration are just as likely to benefit. It seems to be worth a trial in any case where a lengthy period of use of night splints is acceptable to the patient.

Where for economic or any other reasons a sure cure is called for, with the least risk of relapse and no necessity for prolonged treatment or supervision, operation is indicated. Operation is, of course, still available if other methods of treatment fail. In all but a very few patients the results of surgery are excellent, and even these few relative failures can probably be eliminated by careful technique and post-operative care.

Summary

The results of treatment are described in a series of 81 cases of carpal-tunnel syndrome which were kept under prolonged observation. The methods used were immobilization of the wrist at night, local injection of hydrocortisone, and division of the flexor retinaculum. Other recommended forms of therapy are briefly discussed.

Local hydrocortisone is advocated as a diagnostic measure, as a means of rapid alleviation of severe symptoms, and as therapy in a limited number of cases, notably where the syndrome is associated with pregnancy and where it develops acutely after excessive use of the hands. Immobilization yields a satisfactory result in about 40% of cases, whatever their severity or duration. Surgical treatment offers almost certain and permanent relief.

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ACROPARAESTHESIAE AND ACROMEGALY

BY

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The syndrome of acroparaesthesiae due to compression of the median nerve in the carpal tunnel, with the relief obtained by section of the transverse carpal ligament, has recently attracted much attention. It might be expected that diseases causing abnormalities of the carpal tunnel should frequently give rise to acroparaesthesiae, but examples have not often been recorded. Bony lesions, such as a dislocated lunate, and haemorrhage have been reported by Watson-Jones (1949). A neuroma was mentioned by Cannon and Love (1946), though it is not clear from their paper that this was a tumour in the strict sense. The syndrome has been reported in myxoedema (Schiller and Kolb, 1954; Murray and Simpson, 1958) and in acromegaly in nine cases (List, 1932; Woltman, 1941; Cannon and Love, 1946; Kellgren *et al.*, 1952; Schiller and Kolb, 1954). The present paper adds five more.

Case 1

A police officer aged 39 was admitted to hospital under Dr. Michael Ashby in June, 1958. He had always been tall, but acromegalic features had been apparent in photographs for only about 10 years. There had been no increase in the size of his hands during the previous five years. For nine months he had complained of painful tingling in the thumb and middle three fingers of the right hand, principally at night. For two months the left hand had been affected similarly though less severely. His sleep had been disturbed by the attacks.

Examination showed the typical features of acromegaly. There was wasting of both thenar eminences, particularly of abductor pollicis brevis, more marked on the right. There was no sensory loss.

On June 11 Mr. P. T. Savage carried out bilateral carpal-tunnel section. On the right the median nerve was red and swollen, with definite constriction. Similar but lesser changes were seen on the left.

In November, 1958, he reported that he had been completely relieved by the operations, though on examination there was still some thenar wasting. At this time ischaemia produced by inflation of a sphygmomanometer cuff above the systolic blood-pressure (Gilliatt and Wilson, 1953) did produce impairment of sensation over the median area in both arms. This was repeated on several occasions, but the sensory deficit developed only after 15 to 20 minutes. On one occasion, however, a severe attack of pain, identical with his preoperative symptoms, was produced in five minutes in the right arm. The cuff was over the middle of the forearm, and it is interesting that the pain radiated to the elbow above the cuff. It proved impossible to precipitate further attacks by various manœuvres, including inducing venous engorgement or holding the arm dependent.

Case 2

A plumber aged 49 first attended Dr. Ashby's out-patient clinic in September, 1955, complaining of pain and numbness in the hands, occurring mainly at night over the previous 18 months. Acromegaly had been present for 10 years. A diagnosis of mild carpal-tunnel syndrome was made, and as his symptoms subsided with rest no further action was taken. He again attended in September, 1958, because of a recurrence of the acroparaesthesiae five weeks previously. The middle three fingers were mainly affected, more so on the right. The attacks occurred almost entirely at night except that hammering at work would sometimes precipitate one.

Examination showed typical acromegaly. In the hands there was doubtful flattening of the right thenar eminence but definite impairment of sensation of median-nerve distribution on the right and to a lesser extent on the left.

On October 8 Mr. Savage performed bilateral carpal-tunnel section and found that on the right there was definite compression of the median nerve.

Ischaemic tests before operation enhanced the sensory deficit, but only after 17 minutes. When the sphygmomanometer cuff was released the patient could then distinguish between the ulnar-nerve and the median-nerve distribution, as the post-ischaemic tinglings disappeared first in the ulnar area. These findings could be reproduced three months after operation when he was symptom-free in the right hand, but he had had occasional tingling in the left since returning to work.

Case 3

A box-maker aged 47 was admitted under Dr. Ashby on May 19, 1959. She first noticed persistent swelling of her face 26 years ago after an attack of erysipelas. Increase in the size of her hands was noted during the war and of both hands and feet about three years ago. She has required treatment for diabetes since May, 1958 (Dr. A. Bloom), and for dermatitis for nine years.

Pain and tingling in her hands at night first began during the war while working in an aircraft factory. The right hand was affected much more than the left. She had had occasional attacks since then, but none had persisted until the present series, which began in December, 1958. She then had, in addition, permanent roughness of the radial aspect of the ring finger and the whole of the middle finger of the right hand.

Examination showed typical acromegalic features with patches of dermatitis. The only abnormalities in the central nervous system were wasting of the thenar eminences with weakness of abductor pollicis brevis and impairment of sensation of median-nerve distribution. All these abnormalities were greater on the right.

Ischaemic compression of the arm sometimes enhanced the sensory impairment within seven minutes, but occasionally there was no change after a quarter of an hour.

X-ray examination of the skull showed an enlarged pituitary fossa.

The patient was seen by Mr. Savage, who performed carpal-tunnel decompression on July 2, 1959, with relief of symptoms.

Case 4

A man aged 67 was admitted under Dr. A. L. Jacobs in July, 1957. Acromegalic changes were first noted in 1918, the diagnosis being made in 1925. He complained at that time of tingling in the hands. Two courses of radiotherapy were then given to the pituitary.

In July, 1955, he was again seen at another hospital complaining of tingling in the fingers of both hands. This affected mainly the middle fingers, especially at night. There was no motor or sensory loss and no change in the reflexes. A diagnosis of carpal-tunnel syndrome was made.

His complaints on admission were varied, and he soon developed a paranoid state requiring his transfer to a mental observation ward. He has not been seen since.

Case 5

A man aged 53 was admitted under Dr. Bloom in September, 1958. The changes of acromegaly were present in 1942. He was given a course of radiotherapy to the pituitary in April, 1958. In addition he had chronic bronchitis

and emphysema, a rounded mass in the lingula, thought to be a hamartoma, as well as some weakness and wasting of the legs without reflex changes.

In 1954 and again in 1958 he had wakened at night with numbness of his hands, banging them on the bed for relief. All fingers were affected. It also occurred when he was out walking.

No neurological signs were found in the hands. Occlusion of the brachial artery was tolerated for only about seven minutes because of a feeling of severe tightness in the hands and forearms which was apparently similar to his attacks. There was no localization of the paraesthesiae or sensory impairment to any particular area. A diagnosis of carpal-tunnel syndrome was made.

Median nerves of patient with acromegaly showing constriction in the carpal tunnel.

The following case is recorded because a necropsy was performed.

A female clerk aged 53 was admitted under Dr. Ashby on May 15, 1959, as an emergency case. During the evening she had vomited several times and then lost consciousness.

On examination she was deeply comatose, with extensor plantar responses. There was no thenar wasting. A diagnosis of cerebral haemorrhage was made. Her condition steadily deteriorated and she died four hours later.

The previous history was that increase in the size of her hands and feet was first observed in 1933 and change in her features 10 years later. There was no history of pain or tingling in her fingers.

Necropsy showed acromegalic features with an enlarged cystic pituitary gland. Section revealed an adenoma of the anterior lobe which was mainly eosinophil. The anterior carpal ligaments were thickened, with compression of both median nerves (see photograph). Histologically there was marked perineural fibrosis, with moderate epineural and endoneural fibrosis distal to the sites of the constriction. Silver-staining showed moderate reduction in conducting elements distal to the constriction on the right side but only slight reduction on the left.

Discussion

These five patients with acromegaly all developed a syndrome similar to that described by Brain *et al.* (1947). It is perhaps surprising that only nine cases of acromegaly and carpal-tunnel syndrome have been reported in the literature, as it is likely that the real incidence is much higher. Sternberg (1899), in his review of acromegaly, regarded acroparaesthesiae as an early symptom of the disease but one which rarely persisted in the fully developed condition. He quoted one suggestive history and said that thenar wasting might occur. Atkinson (1932) also reported that acroparaesthesiae were quite common.

In the present series occupation did not appear to be important, as only one of the patients is employed in a trade, though the right hand was more severely affected in three cases. In the literature the details are incomplete.

One notable difference from the usual syndrome is the sex incidence. Kremer *et al.* (1953) stated that in their series of patients with the carpal-tunnel syndrome women were affected five times as often as men. Dick and Zakik (1958) gave a 6/1 ratio. In the 14 cases so far recorded there are equal numbers of men and women. We know that the carpal tunnel is smaller in women than in men (Garland *et al.*, 1957), but this difference may well be abolished by the characteristic local overgrowth of bones and ligaments in acromegaly.

The frequent onset of acroparaesthesiae in women around the menopause suggests an endocrine abnormality. Schiller and Kolb (1954) therefore treated three cases of menopausal median neuropathy with oestrogens, with relief of symptoms. A spontaneous remission may have been responsible for this effect.

Other lines of evidence support a soft-tissue component—for example, the considerable spontaneous variations when reviewed over the course of 24 hours or over many years. In the acroparaesthesiae of acromegaly the symptoms are sometimes quickly relieved after treatment of the pituitary either surgically (Schiller and Kolb, 1954) or by adequate radiotherapy (List, 1932 ; Woltman, 1941). The rapidity of response supports the presence of a soft-tissue factor. However, in some patients—for example, Cases 1 and 2 of the present series and Schiller and Kolb's second case—the disease appeared to be inactive at the time of the development of the acroparaesthesiae. Nevertheless, in view of the equal sex incidence of acromegaly and of acroparaesthesiae in acromegaly, the alteration in bones and probably ligaments predisposes to the development of paraesthesiae.

Albright *et al.* (1946) showed that decrease in the volume of the hands and feet of acromegalic patients occurred on oestrogen therapy. The change was attributed to an alteration in the amount of sodium-and-water retention and could be as much as 10% of the initial volume. They further pointed out that active acromegaly resembled the post-menopausal state. In both there is a high serum inorganic phosphorus level and negative calcium and phosphorus balances, with a tendency to osteoporosis. With oestrogen therapy these changes are reversed. There may therefore be a similar mechanism underlying the production of acroparaesthesiae in both conditions—possibly imbalance between oestrogens and growth hormone—producing its effects by sodium retention and increase in the extracellular fluid. Again, there is increased sodium-and-water retention in pregnancy. It is not surprising, therefore, that an increased incidence of acroparaesthesiae in pregnancy has been reported, and usually it has been relieved immediately after delivery (Garland, 1955 ; Heathfield, 1957). Again, in myxoedema the relief of the acroparaesthesiae shows a clear relationship to the clinical response to treatment. Further, relapse to the myxoedematous state may be associated with a return of the acroparaesthesiae, only to disappear again when the patient becomes euthyroid (Murray and Simpson, 1958).

The importance of the anatomical background in acroparaesthesiae is suggested by the dramatic relief

obtained by section of the carpal tunnel—for example, Kellgren *et al.* (1952). This is also supported by the occasional cases where space-occupying lesions are found—for example, a displaced lunate bone (Watson-Jones, 1949). Previous bony injury is often contributory, especially malunion of a Colles fracture (Newman, 1948; Garland, *et al.*, 1957). In addition there is the occasional case where relief is not obtained until an incomplete decompression is remedied at a second operation (Kremer *et al.*, 1953).

Though it is axiomatic that there is local overgrowth of the extremities, by the very derivation of the name acromegaly, the bony changes do not appear to be responsible alone. There is a varying soft-tissue component as well, since some cases are burnt out when first developing acroparaesthesiae. That the two factors are involved is strongly supported by the necropsy findings in Case 6. The constriction of the median nerves was striking, and histologically there is evidence of nerve damage, yet the patient had no symptoms. Apparently the critical soft-tissue component was not present.

The residual space in the carpal tunnel is probably smaller in acromegalics. The development of symptoms in both cases seems, however, to be more dependent on changes in the soft-tissue component. These variations, though possibly small, can be highly critical in a confined space.

Why the characteristic story of hanging the arms out of bed or moving them about should give relief is not so clear. Contraction of the muscles will increase the lymphatic flow and so remove any increase in the extracellular fluid. This would take some minutes to produce its effects, which tallies with the clinical story. Osborne (1959) suggests that venous stagnation and local tissue changes rather than arterial compression are responsible for the symptoms. It is surely ischaemia developing at capillary level which is responsible. Hanging the arm down, however, might be expected to increase the extracellular fluid. It may be that just enough fluid flows into the palm to tip the balance and relieve the pressure. Alternatively, it is well known that when an injured hand is dependent it throbs severely. It is possible that a similar increase in blood supply is sufficient to relieve the anoxia of the median nerve. Stammers (1959) suggests that it is the peripheral vasodilatation during sleep which is responsible for the classical nocturnal occurrence, by adding to the squeeze already present.

It would seem reasonable to conclude that the general thickening of the bones and soft tissues, often so striking in acromegaly, probably reduces the capacity of the carpal tunnel to a critical level, at which a small increase in the extracellular fluid induces anoxia of the median nerve.

Summary

The syndrome of acroparaesthesiae occurring in acromegaly is described in five cases, together with the necropsy findings in one patient who had no symptoms but showed evidence of median-nerve compression. Only nine similar cases have been recorded previously.

The sex incidence is equal in the acroparaesthesiae of acromegaly, compared with the marked preponderance of females in acroparaesthesiae without acromegaly.

It is suggested that the great variation in symptoms of acroparaesthesiae is due to a soft-tissue component acting in the confined space of the carpal tunnel and that this effect is exacerbated by the local overgrowth of the structures forming the tunnel in acromegaly.

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MEDIAN-NERVE PALSY AS A COMPLICATION OF ACUTE PYOGENIC INFECTIONS OF THE HAND

BY

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Since the "carpal-tunnel syndrome" was first described by Brain, Wright, and Wilkinson (1947), many cases of median-nerve palsy due to compression of the nerve as it passes deep to the transverse carpal ligament have been reported. Causes commonly cited include degenerative arthritis due to old fractures of the carpal bones (notably the scaphoid), chronic rheumatoid arthritis, non-specific proliferative tenosynovitis of the flexor tendons, and cases of tuberculous tenosynovitis. All these are *chronic* conditions. Not so well recognized, however, is the occurrence of acute median-nerve compression resulting from severe pyogenic infection of the hand. I have been able to find only one other reference to this condition (Bailey and Bolton Carter, 1955).

These writers described two cases of acute infection of the tendon sheath which subsequently developed median-nerve palsy. Both cases were treated successfully by decompressing the nerve.

Three further cases are described below.

Case 1

A housewife aged 68 was referred to the General Hospital, Birmingham, on January 21, 1958. Three days previously she had developed a painful swelling of her right thumb. She could not remember injuring the part. Pain and swelling

increased, and two days later the swelling had involved all her fingers, the palm, and the anterior surface of her wrist.

On examination her temperature was 100.6° F. (38.1° C.). The thumb and all the fingers were inflamed and swollen. The swelling extended up over the anterior aspect of the wrist. Severe pain prevented both active and passive movements of the fingers. Local tenderness was pronounced over the palm and front of the wrist. There was no evidence of any local cutaneous lesion on any part of the hand. She complained of numbness of her fingers.

Acute streptococcal infection of the hand was suspected. Treatment with systemic penicillin was started and the hand was splinted.

The next day careful examination revealed complete anaesthesia over the whole of the median-nerve area of the lateral three and a half digits and the distal part of the palm. Motor function of the thenar musculature could not be assessed because severe pain and swelling prevented movement of the thumb. Sensation over the distribution of the ulnar nerve in the hand was quite normal. Urgent decompression of the median nerve seemed to be indicated.

Operation.—This was performed under general anaesthesia, in a bloodless field. An incision was made in the crease round the base of the thenar eminence as far as the distal flexor crease of the wrist. It was extended along this in its medial two-thirds, and then a further extension at right angles was made for 2 in. (5 cm.) up the forearm. The subcutaneous tissues were very oedematous. The transverse carpal ligament was completely divided. The nerve was grossly flattened throughout its course deep to the ligament, the upper margin of which had made a well-marked indentation in the nerve. The tendon sheaths were widely opened, releasing a quantity of very thin pus. A swab was taken for culture. The wound was closed, several strands of nylon being used as a drain. The hand was again splinted and treatment with systemic penicillin was continued.

The patient was pyrexial for three days. Culture of the pus revealed the presence of β-haemolytic streptococci fully sensitive to penicillin.

By the fourth post-operative day her temperature was normal, almost all inflammation and swelling had subsided, and movement of the median-supplied thenar muscles could be demonstrated, though weakly. Sensory examination showed patchy return of sensation near the bases of the fingers, but not at the tips.

Physiotherapy was started on the fifth day. Penicillin was continued for two weeks, until all traces of inflammation had disappeared and the wound was completely healed.

Two months after operation function was almost normal. She had a strong and painless grip, and the only abnormality still detectable was slight diminution of light touch sensation over the pulps of the index and middle fingers. Two years later there was minimal blunting of light touch sensation on the pulp of the index finger, and she had no disability even when doing fine needlework.

Case 2

A male Pakistani aged 52 was referred to the General Hospital, Birmingham, on April 3, 1958. Two days previously he had punctured the flexor aspect of his right wrist and the base of his little finger with pieces of wire, which he had promptly withdrawn. Twenty-four hours later he developed pain in the wrist and then the hand.

On examination small puncture wounds at the above sites were noted. There was considerable tenderness in the little finger, together with tenderness and swelling of both palm and dorsum of the hand. An injection of benzylpenicillin was given, and also 1,500 I.U. of A.T.S. The hand was splinted.

The next day the swelling of the wrist had increased. Local exploration at the site of the puncture wound revealed no superficial pus.

On April 5 there was still no evidence of real localization. The hand remained very swollen and tender. Sensory examination revealed slight but definite blunting of light touch and pinprick perception over the median-nerve area in the hand. Motor function could not be adequately assessed because of pain. No surgical action was taken at this stage, however. Tetracycline was given.

On April 7 an acute progressive alteration of median-nerve function was established. There was complete absence of sensation over the whole median distribution. Ulnar- and radial-nerve areas of sensation were normal. It was decided to explore the nerve in the carpal tunnel.

Operation.—This was performed on April 7, under general anaesthesia in a bloodless field. The same incision was used as in Case 1. The transverse carpal ligament was completely divided. The nerve appeared to be only moderately compressed in the tunnel, and there were none of the signs of severe local compression which were noted in Case 1. The tendon sheaths were opened, revealing a lot of thin purulent exudate. A swab was taken for culture. The wound was closed, several strands of nylon being used as a drain. The hand was splinted. Culture of the pus revealed a growth of β-haemolytic streptococci sensitive to penicillin, and also a coagulase-positive *Staphylococcus aureus* and *Streptococcus faecalis* which were insensitive to penicillin and streptomycin but sensitive to tetracycline. He was having both penicillin and tetracycline, in fact, and these were continued.

Local symptoms of pain and tenderness were slow to subside, though wound-healing was rapid. Splintage was continued for 10 days before active movements were encouraged. On April 18 a patchy recovery of perception of pinprick was noted, mainly at the bases of the fingers. Subsequent recovery was very slow. By June 3 he still had not got a full range of active movement, and he complained bitterly of pain in the scar. There was still impaired sensation in the middle finger, but recovery in the other digits was almost complete. At this stage he was lost from follow-up for some time. However, re-examination 12 months later revealed a good late result, with almost full recovery of tendon and nerve function. There was no wasting of the thenar eminence. Abduction and opposition of the thumb were powerful. Flexion of the fingers was slightly limited, but this barely affected his grip, which was only slightly less powerful than that of the uninjured hand. Sensory examination revealed only very slight patchy blunting of light touch and pinprick perception over the median-nerve distribution.

Case 3

A housewife aged 50 was admitted to the Queen Elizabeth Hospital, Birmingham, on December 31, 1954. She complained of severe throbbing pain in the right thumb and index finger, which had become very swollen and inflamed over the course of a few hours. She had had several attacks of shivering. She remembered cutting her thumb and index finger on some "tinsel" six days previously, but had taken little further notice of these apparently trivial injuries. Her doctor had given her an injection of penicillin before referring her to hospital.

On examination her temperature was 101° F. (38.3° C.). She was obviously acutely ill. The whole of the right hand was swollen, the swelling extending to just above the wrist. The thumb and index and middle fingers were principally involved and were very tender. Small, apparently clean, shallow cuts were present on the pulps of the thumb and index finger. There were tender enlarged glands in the axilla.

She was thought to have a rapidly spreading cellulitis of the right hand and forearm, probably of streptococcal type. The arm was splinted and elevated. She was given 1,500 units of antitetanus serum, and put on systemic penicillin and oral tetracycline. Her general condition slowly improved, and her temperature fell to 99° F. (37.2° C.) in three days. During this time her hand became less painful, but the swelling did not subside. On January 4, 1955, she complained of tingling, then numbness of median-nerve distribution, suggesting that the nerve was compressed in the

carpal tunnel. Further swelling slowly developed, together with acute tenderness both in the palm and just above the transverse carpal ligament on the front of the wrist. There was almost complete loss of median-nerve sensation in the thumb and index and middle fingers. Motor function of the short thenar muscles could not be tested because of the extreme swelling and tenderness. On January 7 it was decided to explore the front of the wrist.

Operation.—This was performed by Mr. A. Gourevitch under general anaesthesia, in a bloodless field. An incision was made along the ulnar border of the wrist, and Parona's space was opened. The tissues were all oedematous and a small quantity of blood-stained exudate was evacuated. A second incision was made, curving round the base of the thenar eminence and up to the distal wrist-crease. The palmar fascia and transverse carpal ligament were exposed. The latter was divided completely, exposing the median nerve. No macroscopic evidence of compression was noted, but some further blood-stained fluid was evacuated from here and from the mid-palmar space, which was explored by an incision through the palmar fascia. No frank pus was found. A small rubber drain was placed in each wound and the incisions were closed with silk sutures.

Organisms were not cultured from the swab taken at operation. Nevertheless, antibiotic treatment was continued in view of the persistent inflammatory changes in the hand. These slowly subsided over the next 48 hours, and there was patchy return of sensation except at the tips of the affected digits. Movements were encouraged from this stage as there was gross stiffness of the hand. Improvement was steady but slow. She was allowed home three weeks after operation, at which time sensory recovery was full except for the terminal pulp areas. Physiotherapy was continued for a further two months, during which period hand and finger movements returned almost to normal.

She was seen again recently, five years after her illness. Power of grip was very slightly weaker than on the left. Movements were normal. There was persistent minimal blunting of light touch sensation on the tips of the thumb and index finger, but this caused her hardly any disability apart from, she stated, making her slightly clumsy when doing very fine needlework.

Discussion

In their two cases of the same condition, Bailey and Bolton Carter (1955) suggested that interference with median-nerve function resulted from compression by inflammatory exudate in the radial and ulnar bursae deep to the transverse carpal ligament. They preferred this hypothesis of compression ischaemia to the alternative explanation that the changes were produced by the direct spread of infection to the nerve.

The present series would appear to support their view. Particularly in Case 1 did the appearance at operation suggest compression. In this case and also in Case 2 there was tight distension of the flexor tendon sheaths in the carpal tunnel. The somewhat later onset of nervous signs in Case 3, after the infection was coming under control, also suggests a pressure effect rather than an infective neuritis.

On the basis of the experience of these three patients, and in view of the two similar cases previously described, it is urged that a close watch be kept for signs of interference with median-nerve function in all severe acute hand infections, and particularly in those in which the tendon sheath is involved. Such cases should be treated by division of the transverse carpal ligament as soon as any signs of damage to the median nerve are noted. This division must be complete, and at the same time the ulnar and radial bursae should be opened to drain any infective exudate therein.

Summary

Three cases of acute infection of the hand complicated by median-nerve paralysis are described.

In two patients the tendon sheaths deep to the transverse carpal ligament were shown to be involved in an acute streptococcal infection.

The nerve lesion was probably due to pressure in the carpal tunnel as a result of the acute inflammatory swelling. All three cases were treated by division of the transverse carpal ligament.

I thank Mr. A. B. Watson for permitting me to treat Cases 1 and 2, and Mr. A. Gourevitch for allowing me to publish the details of Case 3; also for their help and encouragement in the preparation of this paper.

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AUTOMATIC CLOTTING-TIMER FOR CONTROL OF ANTICOAGULANT THERAPY

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In the control of anticoagulant therapy there are two basic requisites: first, the laboratory control; and, secondly, the equally important experience needed to prescribe anticoagulant drugs so as to allow for the inevitable changes in the maintenance dose which may occur owing to changes in health, diet, administration of other drugs, etc. Much can be done to maintain adequate anticoagulant control by recognizing these "periods of danger" (Toohey, 1959) and making any necessary changes in the dose as early as possible, and by taking more frequent blood tests during these "periods of danger." Here the great advantage of the physician who actually prescribes the anticoagulant drug seeing the patient at the time the blood test is taken, as opposed to a "postal service," is clearly evident. With regard to the actual anticoagulant drug, there are now available several good oral anticoagulants for the control of both short- and long-term anticoagulant therapy (Toohey, 1959).

Unfortunately, even to-day, after many years of experience with anticoagulant therapy, there is no universal agreement on the best laboratory method for the control of this treatment. Controversy still exists about the relative merits of the two most widely used laboratory techniques—Quick's one-stage technique and Owren's "P and P" method. Quick's one-stage technique has the great advantage of speed and simplicity. Owren's method is more sensitive and also allows more accurate comparison of results between different laboratories. Owren's method, however, has great disadvantages for widespread use: first, the

*Dr. Toohey died on March 21, 1960, after this paper had been prepared.

reagents are not available commercially, and they require some skill and experience in their preparation; and, secondly, when large numbers of patients are being treated the time needed to carry out the tests can be appreciable. Owren (1959) has produced a modification of the "P and P" method—the thrombotest—which can be used with capillary or venous blood and also with citrated plasma. It is unlikely that the use of capillary blood will become widespread, as with capillary blood the test has naturally to be done at the time the blood is taken. This will often be inconvenient for most hospital organizations. The great advantage of the thrombotest will lie in the availability of a commercial reagent which is stable and gives reproducible results.

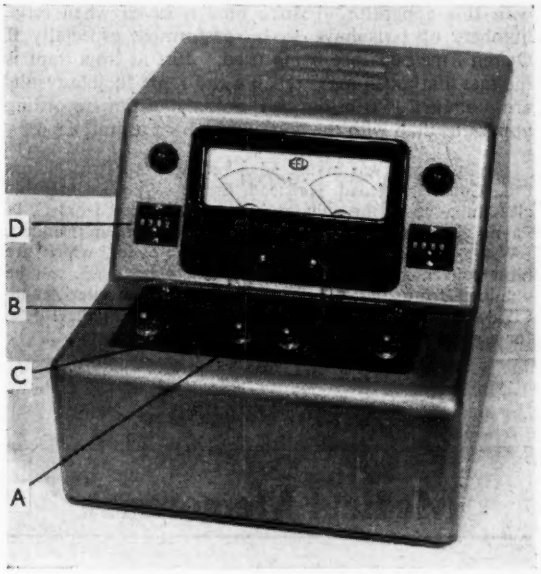
Automatic Time-recording Apparatus

Even with a stable commercial reagent readily available, however, there remains one disadvantage with Owren's method as compared with Quick's technique—that is, the much longer time needed to carry out the tests. As mentioned earlier, when large numbers of patients are being treated (as is likely with the increasing use of long-term anticoagulant therapy) this time-factor is important. To overcome this disadvantage we have devised an automatic time-recording apparatus (see Fig.). This apparatus can be used for measuring the clotting-time of plasma such as the calcified plasma clotting-time, Quick's one-stage technique, Owren's original "P and P" method, and the more recently introduced thrombotest using plasma.

All these tests are carried out in the usual manner, except that glass tubes of special size to fit the apparatus are used. (It is also important to use sodium citrate† and not oxalate in collecting the blood sample.) As soon as the calcium is added, the time-recorder is started by moving switch A. The tube, the end being closed by the tip of the finger, is completely inverted once to mix the contents thoroughly, and the tube is then inserted into the aperture B. By turning the galvanometer sensitivity control 4, the galvanometer needle is adjusted midway between the two marks on the galvanometer scale. A few seconds are now allowed to elapse to permit of any slight drift that may occur. This drift is negligible in most cases if citrate is used as the anticoagulant in collecting the blood sample; if, however, oxalate is used a considerable drift may occur for several seconds owing to precipitation of calcium oxalate.

Once the galvanometer needle is steady for a few seconds the time-recording switch A is moved in the opposite direction to that previously. This second movement brings into play an automatic cut-out. When clotting starts a turbidity develops in the plasma. This is one of the earliest changes to occur, and it develops immediately before an actual clot is visible to the naked eye. This turbidity causes the galvanometer needle to shift, and this in turn brings the automatic cut-out into action and stops the time-recording apparatus. The clotting-time can then at once be directly read from clock D in seconds. The apparatus has a temperature-regulating mechanism to allow tests to be carried out at 37° C.

Once the automatic timer is brought into action no further attention is needed. The operator may leave the laboratory, and when he returns the result of the test is clearly recorded. More important, the apparatus has been devised to allow duplicate tests to be carried out simultaneously, so that once one test has been set up the second test can be started in the second part of the apparatus without waiting for the result of the first test. Subject only to the number of machines available, any number of clotting-tests can be carried out by one operator without the need to await completion of any single test.



Time-recording apparatus. A, time-recording switch. B, aperture for insertion of tube. C, galvanometer sensitivity control. D, clock.

Before the automatic cut-out is brought into action the galvanometer needle may be freely moved without stopping the time-recorder. Once, however, the automatic cut-out is brought into the circuit care must be taken not to move the galvanometer needle beyond the indicated marks on the galvanometer scale, otherwise the time-recorder will be stopped and thus give a false reading.

This apparatus not merely saves a good deal of time; it also results in standardization in reading the results of clotting-time, which is equally, if not more, important. Some operators find reading the end-point of clotting difficult until they have had considerable experience in the use of clotting techniques. This is evident from the obvious discrepancies between the results obtained in the reading of results by different operators, who are nevertheless using the same techniques and the same reagents. The apparatus described here eliminates any discrepancies in the reading of the end-point of clotting times and gives more accurate standardization of results. In over 500 tests done simultaneously with this apparatus and with the usual hand-water-bath technique, the apparatus gave more accurate and reproducible results.

Summary

An apparatus is described for automatically recording the end-point of clotting when blood-clotting tests are carried out using plasma. Quick's one-stage technique, Owren's "P and P" method and thrombotest, and re-calcified plasma clotting-times can all be carried out

†3.13% sodium citrate replaces the potassium oxalate.

with this apparatus. Much time is saved when large numbers of tests have to be performed, especially if Owren's methods are being used. Just as important is the fact that much more reliable and reproducible results are obtained by using this automatic time-recording apparatus than with the hand-water-bath technique.

The apparatus was made for us by Evans Electroselenium Ltd., Colchester Road, Halstead, Essex. Cheap disposable glass tubes to fit the apparatus can be obtained from C. E. Payne & Sons Ltd., 131, Clapham High Street, London, S.W.4. Fine-pointed accurate 0.2-ml. pipettes, which are most convenient to use with the small glass tubes, can be obtained from Baird & Tatlock Ltd., Freshwater Road, Chadwell Heath, Essex. We thank Evans Medical Ltd. for a grant towards the development of this apparatus.

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Medical Memoranda

Purpura After Administration of Piperazine

During recent years piperazine has replaced many other anthelmintics in the treatment of ascariasis and oxyuriasis. It is supposed to be non-toxic. Recently we observed a patient in whom a single 4.8-g. dose of piperazine citrate was followed by extensive purpura. We have not come across any other similar report in the medical literature so far. A brief account of the purpuric episode is given.

CASE REPORT

A girl aged 10 years was admitted to the E.N.T. wards of Hamidia Hospital, Bhopal, on January 15, 1959, complaining of epistaxis and bleeding from the gums for two days. At this stage she and her mother failed to co-operate in elicitation of a proper history. Anterior rhinoscopy showed a large number of punctate bleeding-points on the anterior part of the septum and inferior turbinate on both sides. Bleeding was moderate in amount. Examination of the buccal cavity revealed bleeding from the gums; posterior rhinoscopy did not show any more bleeding-points, and there was no bleeding from the pharynx and larynx. Skin of the whole of the body showed discrete purpuric spots. In the wards a gross haematuria was also found.

Investigations.—R.B.C., 3,400,000/c.mm.; haemoglobin, 62%; total W.B.C. count 6,400/c.mm. (polymorphs 54%, lymphocytes 40%, large monocytes 5%, eosinophils 1%); bleeding-time, 2 min. 30 sec.; coagulation time, 4 min. 54 sec.; prothrombin time (modified Quick's method using "thrombokinase" calcium tablets) 20 sec. (control 20 sec.); blood platelet count, 135,000; Hess's capillary test, positive. Urine: large number of red cells and albumin + +. Stools: N.A.D.

She was given vitamin C, 500 mg. intravenously and 100 mg. t.d.s.; vitamin K, 10 mg. t.d.s.; "styptobion," 1 tablet t.d.s., calcium lactate, 10 gr. (65 mg.) t.d.s. "Argyrol" nasal drops, gargles with Condy's fluid, and mist. bromide were also administered. Her condition remained stationary for four days, and on January 19 she was transferred to the medical wards. By this time the epistaxis had stopped. Purpuric spots were still present extensively over the trunk and extremities. She looked very weak, and pallor was marked. At this stage urgent blood grouping and matching were done, and a donor was found, though because of her subsequent recovery the blood transfusion was not administered. In the medical wards she was given vitamin C, 500 mg. intravenously daily; vitamin K, 10 mg. intramuscularly six-hourly; and "coagulen-Ciba," 1 ampoule intramuscularly six-hourly. Haematuria and epistaxis had ceased by January 20, though purpuric spots over the trunk and extremities were still appearing.

On January 22 closer questioning revealed that the patient had had 4.8 g. piperazine citrate in a single dose eight days before the onset of symptoms, on the prescription of a local practitioner who suspected ascariasis on clinical grounds only. The patient did not pass any worms subsequently, but on January 13 she developed epistaxis. After the elicitation of this history all previous treatment was stopped and "synopen" tablet 1 t.d.s. was given on the presumption that the purpura might have been due to piperazine allergy. By next day all bleeding had stopped, the purpuric spots were fast disappearing, and Hess's capillary test was negative. By January 26 all purpuric spots had disappeared, and clinically nothing abnormal could be detected. Serial investigations revealed that the platelet count on January 21 was 135,000/c.mm., and on February 3 it was 350,000/c.mm. The bleeding-time and the clotting-time on February 3 were 1 min. 6 sec. and 4 min. 5 sec. respectively. Subsequently the patient made an uneventful recovery. All treatment was stopped on January 26. The patient was kept under observation in the ward for another 15 days, being discharged on February 11.

COMMENT

The anaphylactoid purpuras are diagnosed because of the absence of blood changes. Thus the bleeding-time in such cases is normal, and there is no diminution in platelet count. In our patient, though the platelets were reduced to 135,000/c.mm., they never fell below 40,000/c.mm.—a level below which bleeding is generally observed to begin (Whitby and Britton, 1957), though exceptional cases are known to exist in which bleeding had occurred at counts exceeding 40,000/c.mm., in all probability because of concomitant vascular damage. Though a clot-retraction test was unfortunately not done in this case, the bleeding-time was within normal limits throughout, and it seems unlikely, therefore, that thrombocytopenia was mainly responsible, if at all, for the symptoms. The purpura must have been due to vascular damage. The capillary endothelium and platelets are supposed to be antigenically similar, and it seems that the platelets were also reduced because of the same allergic phenomenon. Allergic thrombocytopenia is known to occur after administration of quinine, quinidine, "sedormid," thiouracil, methoin, and sulphonamides, and no doubt the same antigen can damage both platelets and capillaries.

So far, we are unaware of any published case of purpura after piperazine administration, and it is interesting to record that a supposedly innocent substance like piperazine, which is in extensive use, can precipitate a severe allergic purpura. In this patient the diagnosis of drug allergy was not in doubt, because of the onset of symptoms eight days after administration of the drug, and because of other negative laboratory findings already discussed. An experimental reproduction of purpura after readministration of the drug was not considered worth while because of the hazards.

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Reviews

BEHAVIOUR AND THE BRAIN

Brain, Memory, Learning. A Neurologist's View. By W. Ritchie Russell, C.B.E., M.D.(Edin.), D.Sc.(Oxon.), F.R.C.P. (Edin. and Lond.). (Pp. 140+xii; illustrated. 18s.) Oxford: Clarendon Press. London: Oxford University Press. 1959.

Ritchie Russell has been brave enough to consider seriously the view that all aspects of human behaviour depend upon functioning of the brain. He discusses the profound implications of this view quietly and modestly, and the power of his book derives from the fact that within a strictly professional framework it shows the contribution that neurology can make to some of the most pressing problems of human conduct.

Fellow neurologists turning quickly through will at first see case reports of conditions with which they are familiar—retrograde and post-traumatic amnesias, epilepsies, frontal-lobe lesions, and the like. If they read carefully, however, they will find that these cases are made to illustrate a view of cerebral physiology which, though it cannot be detailed, is yet in outline a complete account of the basis of behaviour. The physiologist will at first complain that there are no elaborate records of action potentials or E.E.G.s and that such human experiments are mostly uncontrolled. Russell knows this as well as anyone, but he also knows that for study of the more subtle working of the brain man is in some ways the animal of choice. The discussion of memory, for example, provides a striking series of pieces of evidence that cortical memory patterns "require a strong play-back action from the hippocampal system" before they can be "consolidated." It is satisfying, if surprising, to find that neurologists provide at least as much evidence about memory processes as do psychologists. Russell gives valuable data about the relative lengths of retrograde and post-traumatic amnesia. He comments on the strange fact that the former may cover a long period, the latter a few seconds, and clearly the changes involved in the two are different. Still further exact data are needed, but already there are enough to allow him to make an important contribution to knowledge of the growth of memory stores by their continued reinforcement.

Of course, at many places one asks for further data and elucidations of meaning. Russell is often aware of the difficulties of terminology, but does not always pursue them to the extent of seeking to improve them. In discussing epilepsy he says "normal neuronal activity becomes uncontrollable," but does not discuss by whom or what it is normally "controlled." Again, reading between the lines one concludes that he is sceptical about referring phenomena to some subthalamic "centrencephalic" system, but his discussion of this is all too brief.

However, it is unreasonable to complain. A great merit of the book is its almost telegraphic brevity—which yet preserves an elegant style. Besides discussing technical matters, Russell makes many bold suggestions as to the possibility of improving our brains. It will do good in many places to hear the suggestion from him that "high intelligence may be more acquired than inherited." He ends the book with a splendid affirmation of the hope that lies in study of "the incredible possibilities for development that are present in every child's brain."

J. Z. YOUNG.

A PRINCE OF DISEASES

The Clinical Syndrome of Diabetes Mellitus. By John Lister, M.A., M.D., M.R.C.P.(Lond.). (Pp. 234+xii; illustrated. 35s.) London: H. K. Lewis and Co., Ltd. 1959.

There is hardly a tissue or an organ in the body on which diabetes may not have its repercussions; for the general physician it is, therefore, the prince of diseases, and the lifelong attenders at diabetic clinics provide a wealth of material from which to study the natural history of disease processes and the medico-social problems which inevitably arise. It has been well said "that one who knows diabetes and all its complications knows medicine"—not only its science but its art. To those physicians, like Dr. John Lister, who have become intensely interested in this fascinating disorder there comes almost inevitably the urge to be evangelists on the subject and to write books about it—long ones for specialists like Joslin's, short ones for patients like Lawrence's, or medium ones like this work for students and practitioners.

In this book the diagnosis of the syndrome, and its complications and its medico-social aspects, are dealt with methodically and most competently. The chapter on the stabilization of the diabetic, or the education of the patient in the control of his disease, only comprises 25 out of a total of 225 pages and is the least satisfactory part of the book; the practitioner will not find a great deal in it to assist him to control his diabetic patients. No detailed instruction, for example, is given as to which of the urine specimens should be tested for glucose or the significance to be attached to the results. Advice is simply given to increase or decrease the dose of insulin "according to the urine tests." Many physicians will disagree with the author's enthusiasm for lente insulin, and the two and a half pages in which the oral hypoglycaemic agents are dismissed are surely inadequate in a modern book. The treatment of diabetic keto-acidosis is, however, admirably described. At the end of each chapter a useful list of references is given, but some of these are poorly chosen and outdated. The book is well produced, well illustrated, and well printed upon good paper, and is not unduly expensive.

D. M. DUNLOP.

MALARIA IN MALAYA

Malariology. With Special Reference to Malaya. By A. A. Sandosham, L.M.S.(S'pore), Ph.D.(Lond.), F.R.E.S., F.L.S., F.Z.S., F.R.M.S. (Pp. 327+xix; illustrated. 35s.) Singapore: University of Malaya Press. London: Oxford University Press. 1959.

This work is essentially a teaching manual addressed to undergraduate medical students of the University of Malaya, in which the author is professor of parasitology, and to postgraduate students taking the diploma course in public health. It is in six sections, the first of which contains a brief account of the history, climate, population, and topography of Malaya and of the numerous researches carried out in that country in the fields of entomology, protozoology, and chemotherapy. The second is concerned with certain basic biological information regarding zoology and haematology. The remaining sections are devoted to the natural history of malaria and of anopheline mosquitoes, malaria surveys, and malaria control and prevention.

There are five appendices dealing with microscopical, haematological, and entomological technique, and the

identification of malaria parasites and of the anopheline species of Malaya. The text is embellished with a number of excellent coloured plates depicting the various species of parasite. The author puts forward no claim to originality and has drawn freely on the publications of the many distinguished workers in the field of malariology for which Malaya is famous. Although in most of the municipalities, rubber plantations, and industrial areas of Malaya malaria has been brought under effective control, the disease still remains one of the country's major health problems, more than 60% of the population of certain rural areas being infected. There is therefore an urgent need for trained personnel to undertake the control and eventual eradication of malaria on a country-wide scale.

This book fulfils admirably the purpose for which it was written, and will be welcomed by all who are concerned with the malaria problems of Malaya. Its value is enhanced by the scholarly foreword contributed by Dr. J. W. Field, late director of the Institute for Medical Research, Kuala Lumpur, and one of the country's most distinguished workers in the field of malariology.

GORDON COVELL.

SCHOLARS' EXODUS

A Defence of Free Learning. By Lord Beveridge. (Pp. 146 +xiv. 18s.) London: Oxford University Press. 1959.

This book is an account of the measures which were taken to help the European scientists and scholars who had to flee to this country from persecution and death for racial, religious, or political reasons in the years before the last war. It is not so much a book as the raw material of history—accounts of the formation of committees, letters to *The Times*, campaigns to raise funds, refugees' stories, and so forth. The exodus began in Germany in 1933, swelling to a torrent as it embraced all the countries dominated by Hitler. It was swollen by refugees from Mussolini's Italy, Franco's Spain, and Stalin's Russia after the assassination of Kirov. The book deals with the arrangements made for some 2,600 men and women who qualified as scholars and scientists, a small proportion only of the total number of refugees. How great is the folly of tyrants! Of the men who fled to this country four won Nobel Prizes and 32 became Fellows of the Royal Society.

A multitude of emotions are aroused by reading this book. There is pride at the work of men like Beveridge, Rutherford, and the quiet C. S. Gibson of Guy's, who were prepared to give up so much time to help the displaced scholars. There is sympathy with men who, in middle or later life, lost not only established positions but everything and were forced to begin life anew. There is shame at the indiscriminate internment of the refugees in this country in 1940, and for the further loss and looting of their possessions which occurred in a few unfortunate instances. And finally, as one reads in the newspapers to-day of brutal murders and violence to wayfarers, of the senseless ravages of hooligans and the arrogance of elected councils, there is the realization that the evil passions which dispersed the refugees are still not far below the surface of our civilization, and that free learning is a heritage that must continually be cherished if it is to be preserved.

L. J. WITTS.

3,000 LAMINECTOMIES

The Degenerative Back and its Differential Diagnosis. By P. R. M. J. Hanraets, M.D. (Pp. 690; illustrated. £5 5s.) London, Amsterdam: Elsevier Publishing Company. 1959.

The clinical syndrome of low-back pain with or without concomitant pain in the leg may result from a variety of disease processes and affects a large proportion of individuals at some time during their lives. Fortunately the symptoms are usually of short duration, and only in a small minority do they persist in a severe enough form to warrant operative treatment. Dr. Hanraets' experience of 3,000 laminectomies performed for this condition is therefore remarkable, and one must be grateful to him for recording his observations and ideas in this book with its many illustrations and closely argued text.

By starting with the false premise that all pain not accurately localized must result from irritation of nerve roots he arrives at a concept of low-back and radicular pain which by definition must be produced by disorders in the spinal canal or intervertebral foramina. Thus the subject is viewed, as it were, from the depth of the wound. However, the problem of pain in the back obviously involves a great deal more of the body and mind of the patient, and in an endeavour to be comprehensive the author discusses many other matters. These range from "status dysrhaphicus" to "diseases of the bony tissues." In the latter osteoporosis and osteomalacia are confused and malacia attributed to endocrine disorders. This is perhaps the best indication of how useful and informative this book can be.

J. H. KELLGREN.

ELECTROLYTE METABOLISM

Clinical Disorders of Hydration and Acid-base Equilibrium. By Louis G. Welt, M.D. Second edition. (Pp. 336+xvi. 50s.) London: J. and A. Churchill, Ltd. 1959.

This is the second edition of a book which first appeared in 1955, written by a recognized authority on electrolyte metabolism. In introducing the new edition the author disarmingly says that he "thinks he has learned how to present some of this material more precisely and more clearly than he did four years ago." This seems to me a just claim; the new writing has mellowed into clarity, and the first part of the book is now a readable account of the physiology of fluid-volume and acid-base balance. The second part of the book, on clinical considerations, remains something of a jumble, though it has been enriched by a good account of paediatric problems contributed by Dr. R. W. Winters. It is difficult to give a good account of dehydration and oedema on the one hand, and of acid-base disturbances on the other, without also dealing more fully with disturbances of potassium metabolism, which can have a critical influence both on fluid-volume and on acid-base balance. It is, for example, somewhat artificial to bring in familial periodic paralysis, laying emphasis on sodium retention (p. 203), but with no general account of the factors which influence the distribution of potassium between cells and extracellular fluid. The information in this book is sound and detailed; but it falls short of a readable comprehensive account of fluid-balance, being limited—not unreasonably, perhaps—to what is promised in its title.

D. A. K. BLACK.

CATHARSIS

Honour a Physician. By Philip Auld. (Pp. 270. 16s.) London: Hollis and Carter. 1959.

One of the several G.P.s featured in this documentary said to the drunken alderman who had called him out of bed at three in the morning, "I'm writing a book explaining how the N.H.S. destroyed the family doctor. I'm calling it Vermin Versus Vocation." The message of the book is that in the industrial north "the idle, the greedy, the dirty, the lying, the treacherous, the lecherous, the drunken, the thieving, the unreliable, the bullying, the sycophant . . ." have taken the heart out of the family doctors, some of whom emigrate, some go into industrial medicine, some ca' canny like their work-shy patients, some take to medical politics, and one joins his uncle in the fish-and-chip business. The publisher's blurb claims that the book is "riotously funny and devastatingly accurate." I failed to get a laugh out of it, and, as for accuracy, my experience declares it to be unrepresentative.

No doubt the G.P. in an industrial practice has a case which requires a hearing and which demands a remedy, but the author wrecks his case by overstatement. There is only one just man in this Sodom of the North, and the recital of the wrongs imposed by evil patients on these frustrated and resentful doctors engenders a tedium which impels the reader to say a word for mankind. One can only hope that Philip Auld feels the better for his notable catharsis.

D. V. HUBBLE.

PHYSIOLOGISTS TALKING

The Central Nervous System and Behavior. Transactions of the First Conference, February 23, 24, 25, and 26, 1958. Edited by Mr. A. B. Brazier, Ph.D. (Pp. 450; illustrated. $5.25.) New York: Josiah Macy, Jr., Foundation. 1959.

Nine American physiologists met under the chairmanship of Professor H. W. Magoun to collate knowledge gained in Russia and America on the neural basis of behaviour. The first part of the work is a long and interesting historical account of Russian physiology in pictorial form. There must have been a tape-recorder going throughout the conference, though, for the rest is a verbatim, unexpurgated transcript which has the bewildering inconsequentiality of police court evidence. Here is an example taken at random from p. 274:

"*Fremont-Smith:* Is the minimum threshold that is noticeable the one that produces pleasure or discomfort?

"*Lilly:* Our only criterion of 'noticeable' is his performance, so that is it.

"*Teuber:* I was just wondering how the porpoise was pushing the lever.

"*Lilly:* With his beak. As you well know the porpoise hasn't a proper nose. The 'nose' is the blow hole. Its jaws are stretched out as if they were a beak."

There are over 300 pages of that sort of thing, reasonable enough at the time, but absurd perpetuated in print. Critical editing could have produced a readable account of an interesting conference.

DENIS WILLIAMS.

"What the reporter in our time seems to need is an Emancipation Proclamation which would guarantee him the right of interpretative comment in the due process of fact-gathering. What the editor needs is a Magna Carta of his own which would allow him—nay, oblige him—to place the interests of the obvious truth no lower than loyalty to the gathered facts." (From "Publicity and Public Affairs" by Melvin J. Lasky, *The Listener*, May 19, 1960, p. 891.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Conquest of Age. The Extraordinary Story of Dr. Paul Niehans' Research. By Gilles Lambert. (Pp. 220. 18s.) London: Souvenir Press, Ltd. 1960.

Pharmaceutical Directory of India 1959. Compiler and Production Manager: S. A. Sarkar. General Manager: J. A. Ebrahim. (Pp. 262. 40s.) Bombay: Star Publications. 1960.

Sex Differentiation and Development. Proceedings of a Symposium held at the Royal Society of Medicine, April 10–11, 1958. Memoirs of the Society for Endocrinology No. 7. Edited on behalf of the Society by C. R. Austin. (Pp. 198+x; illustrated. 45s.) Cambridge: Cambridge University Press. 1960.

Das Parkinson-Syndrom: Klinik und Therapie. By Kurt Hartmann-von Monakow. (Pp. 152; illustrated. Sw. fr. 24.) Basle, New York: S. Karger. 1960.

Il Libro della Salute. By Filiberto Chenal. (Pp. 95. L. 1,000.) Monza: Scuola Tipografia Artigianelli "Pavo niani." 1959.

Die Pocken: Erreger, Epidemiologie und Klinisches Bild. By Professor Dr. A. Mayr. Foreword by Professor Dr. E. Rodenwaldt. (Pp. 295+xii; illustrated. DM. 64.) Stuttgart: Georg Thieme Verlag. 1960.

A Symposium on pH and Blood Gas Measurement: Methods and Interpretation. Edited by Ronald F. Woolmer, V.R.D., B.A., B.M., F.F.A.R.C.S. Assisted by Joy Parkinson, B.A. (Pp. 210+viii; illustrated. 30s.) London: J. and A. Churchill, Ltd. 1959.

Bedside Diagnosis. By Charles Seward, M.D., F.R.C.P.(Edin.). Fifth edition. Foreword by Lord Cohen of Birkenhead, M.D., D.Sc., LL.D., F.R.C.P., F.A.C.P., F.F.R. (Pp. 479+xix; illustrated. 25s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

Peptic Ulceration. A Symposium for Surgeons. By Charles Wells and James Kyle, M.B., M.Ch., F.R.C.S., F.R.C.S.(I.). Foreword by Lester R. Dragstedt. (Pp. 260+xi; illustrated. 42s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

Pediatric Dermatology. By Henry H. Perlman, M.D., Phar.D. (Pp. 477+xii; illustrated. £6 15s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1960.

The Biosynthesis and Secretion of Adrenocortical Steroids. Biochemical Society Symposium No. 18 held at Senate House, University of London, February 14, 1959. Organized by J. K. Grant. Edited by F. Clark and J. K. Grant. (Pp. 112+vii; illustrated. Paper edition 15s.; Cloth edition 25s.) Cambridge: Cambridge University Press. 1960.

The Year Book of Drug Therapy (1959-1960). Edited by Harry Beckman, M.D. (Pp. 570+liii; illustrated. 64s.) Chicago: Year Book Publishers. London: Interscience Publishers, Ltd. 1960.

Praktische Operationskunde und Instrumentenlehre. Leitfaden für das Operationspersonal. By Harro Seyfarth and Elly Jaeger. Second edition. (Pp. 464+xix; illustrated. DM. 36.70.) Jena: VEB Gustav Fischer Verlag. 1960.

Problèmes de Réanimation. Journées de Réanimation Médico-Chirurgicale. Nancy, April 25-26, 1959. Compte-rendu de Rapports, Communications et Discussions. Edited by Professor P. Michon and Professor A. Larcan. (Pp. 405; illustrated. NF. 30.) Paris: G. Doin et Cie. 1959.

Pathogenesis and Treatment of Occlusive Arterial Disease. Proceedings of a Conference held in London at the Royal College of Physicians of London, November 13-14, 1959. Edited by Lawson McDonald. (Pp. 237+xii; illustrated. 25s.) London: Pitman Medical Publishing Co., Ltd. 1960.

Differential Diagnosis for Practitioners in the Tropics: A Clinical Handbook. By W. H. Jopling, M.R.C.P.(Lond.), M.R.C.P.(Edin.), D.T.M.&H.(Eng.), in collaboration with Sir Philip Manson-Bahr. (Pp. 159; illustrated. Issued free of charge.) London: FBA Pharmaceuticals, Ltd. 1960.

Leukaemia: Research and Clinical Practice. By F. G. J. Hayhoe, M.A., M.D.(Cantab.), M.R.C.P.(Lond.). (Pp. 335+viii; illustrated. 80s.) London: J. and A. Churchill, Ltd. 1960.

Atlas of Anatomy and Surgical Approaches in Orthopaedic Surgery—Upper Extremity. By Rodolfo Cosentino, M.D. (Pp. 192+xiv. 84s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

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ACCEPTANCE OF GOVERNMENT'S OFFER

The Representative Body (R.B.), which lays down the policy of the B.M.A., at a special meeting last week voted by a large majority in favour of the following motion put before it by Dr. S. Wand, the Chairman of Council:

1. That the offer of the Minister, as made in his statement to Parliament and as amplified by his letter of April 5, be accepted.

2. That the Minister's invitation to enter into detailed consideration by means of Joint Working Parties be accepted without delay.

3. That the outcome of these discussions be reported to the Representative Body for consideration.

The R.B. was informed that the Central Consultants Committee of the B.M.A., the Joint Consultants Committee, and the Conference of Representatives of Local Medical Committees had agreed to accept the Government's offer. The Conference met in the two days preceding the meeting of the Representative Body; reports appear in this week's *Supplement*.

All the various professional groups—B.M.A., Royal Colleges and Corporations, and autonomous committees—have accepted what has been widely and accurately described by the convenient American expression "package deal." But the Conference of Representatives of Local Medical Committees at one stage carried by 112 to 71 votes a motion urging that access to the Review Body "be as of right and not at the discretion of the Government." When it was realized that this would remove something from the package which is the subject of the deal, the Conference passed the following motion in substitution:

That failing a full and satisfactory assurance that the Government will pass at once to the Review Body any representations from the profession, the profession should press for equal rights with the Government in the matter of direct access to that Body, but considers that the assurance of the Minister constitutes that right.

At the Representative Meeting a number of motions were on the order paper pressing for direct access to the Review Body. But when these and any other motions or amendments were brought up which were ruled as upsetting the package deal, and would, if passed, therefore nullify acceptance of the financial proposals, the R.B. voted against them. The Government has insisted that the profession should accept the whole of the majority report of the Royal Commission if it is to get the benefit of any part of it. These are the plain and simple facts which no amount of eloquence or euphemism can disguise.

The outstanding feature of the Representative Meeting was the able presentation of the case to it by Dr. S. Wand, Chairman of the B.M.A. Council. It is no exaggeration to say that had it not been for him the financial proposals of the Royal Commission would not have been as satisfactory as they are, because inevitably they had to be based on the Spens–Danckwerts formula. The various groups within the profession, however much they may dislike certain items of these proposals, have surely been right to accept them as a reasonable outcome of a most conscientious and detailed examination by the Royal Commission of a highly complicated problem. All those who gave evidence for the profession to the Commission deserve the congratulations of their colleagues in the N.H.S. And if the profession is rightly grateful to them it should also be grateful to those who served on the Commission under the chairmanship of Sir Harry Pilkington. And, perhaps, the profession may also pass a silent vote of thanks to Sir Will Spens and Mr. Justice Danckwerts, but for whom the present financial settlement would not have been reached.

The Government has left the profession to settle for itself whether or not it should accept the Commission's proposal—differential payments for general practitioners. Working parties will sort out such problems as distribution. From the outset, therefore, it soon became clear that there was going to be no bickering or bargaining over betterment factors or the merits of big lists. These things had been thrashed out by the profession's representatives before the Royal Commission, and by and large they were prepared to accept the Commission's recommendations as something conscientiously and fairly arrived at by careful examination of the evidence before it.

Commenting on the Report of the Commission in the week of its publication, the *Journal*[1] said that the profession "would above all welcome the beginning of a new era in which it could co-operate in a fruitful partnership with the State in evolving a National Health Service in which doctors would be content to work at their job of looking after the ill and injured." We believe this reflected a widely held opinion. The Government's response was to offer a package deal. It has said plainly that the profession will get the money offered *only if* it accepts the Review Body as

[1] *Brit. med. J.*, February 13, 1960, p. 487.

proposed in the majority report. It is true it has assured the profession it will pass on to the Review Body the profession's wish for direct access. No one questions the sincerity of the assurance.

In its report to the Special Representative Meeting, the Council said this: "The Review Machinery recommended by the Association in its evidence to the Royal Commission called for a special committee to be appointed by the Prime Minister, and for its terms of reference and composition to be agreed between the Government and the profession. Furthermore, the Association's evidence drew attention to the necessity for direct access to the Review Body by the profession." Later in its report the Council observed "that likewise the profession would need to be certain of its right to appear before the Review Body to present its case whenever it chose and to examine or comment upon any statistical data before the Review Body." The Government has promised to make a recommendation to the Review Body that the profession should be given the opportunity to present their arguments orally to it. As the report of the Conference and of the Special Representative Meeting in this week's *Supplement* shows, there is widespread anxiety about this question of direct access, coupled with dislike of the idea that the Government insisted that the Commission's report should be accepted *in toto*. This was forcibly expressed by the speaker for the South Shields amendment. As reported, the Representative for South Shields said, "Financial considerations apart, there should be an opportunity of discussing the report with the Government in order to safeguard the principles and future of the profession."

Much of the disquiet that has been expressed in these columns would have been allayed if the Government, in addition to giving its assurances about passing to the Review Body the wishes of the profession, had not at the same time insisted upon the profession accepting the package deal. Following the helpful lead given some time ago by Lord Moran, the profession itself advocated the setting up of some kind of review mechanism for the future. In doing this it tacitly accepted the demise of the two Spens Reports. The profession in fact took the initiative in seeking some way of avoiding the recurring financial crises over pay for doctors in the N.H.S. As a "monopoly employer" (the phrase appears in the Report of the Commission) the Government could have introduced the sense of partnership by saying: "Now the pay question is settled, let us discuss the Review Body which in principle, we both agree, is a good thing." But the monopoly employer has said, "You will have the money only if . . ." This, in the *Journal's* view, is an abuse of power and accounts for the pessimism which Sir Robert Platt in this week's *Supplement* (p. 324) criticizes us for entertaining. And he barbs his shaft by calling the title of the leader in the *Journal* of May 14 "undignified." The title was "Package Deal." What Sir Robert in effect is saying is that the package deal (a description of the Government's offer widely used by the profession's leaders and not invented by the *Journal*) is undignified. If the phrase was undignified, then so surely was the thing itself.

FAMILIAL INTESTINAL POLYPOSIS

Adenomatous polyps of the large intestine are not uncommon in childhood. Usually the polyp is single; in about a third of the cases there are several scattered polyps, and in about 1 case in 20 they are numerous—the condition is known as "polyposis."[1] The clinical effects of polyposis are that the polyps may erode and bleed (but seldom severely); if in the small intestine they may cause intussusception; and, most important, carcinoma may develop in one or more of the colonic or rectal polyps.

Three forms of polyposis are known which are clinically and genetically distinct. In the commonest form only the colon and rectum are affected and there are no associated abnormalities. In the second form the polyposis is similar, but in addition there are multiple epidermoid cysts, fibromata, and osteomata. The name "familial intestinal polyposis" is perhaps best confined to these two varieties, and a large majority of patients so affected will develop carcinoma if untreated. In the third form of polyposis, Peutz's syndrome, polyps are present in the colon and rectum, but are most numerous in the small intestine and are also found in the stomach; in addition, there is a characteristic spotty pigmentation of the skin, especially round the mouth, the lips, and the buccal mucosa. In all three conditions the pattern of inheritance is that given by dominant genes. Consequently, on the average, half the children of those affected become affected themselves. But, since each condition breeds true, the three mutant genes must be distinct from each other.

In all three conditions sporadic forms occur, which may reasonably be attributed to a fresh mutation.

[1] Gross, R. E., *Surgery of Infancy and Childhood*, 1953, Philadelphia.
[2] Dukes, C. E., *Ann. Eugen. (Lond.)*, 1952, **17**, 1.
[3] Reed, T. E., and Neel, J. V., *Amer. J. hum. Genet.*, 1955, **7**, 236.
[4] Gardner, E. J., and Plenk, H. P., ibid., 1952, **4**, 31.
[5] Dormandy, T. L., *New Engl. J. Med.*, 1957, **256**, 1093.
[6] —— ibid., 1957, **256**, 1141.
[7] —— ibid., 1957, **256**, 1186.
[8] Oldfield, M. C., *Brit. J. Surg.*, 1954, **41**, 534.
[9] Cole, J. W., and Holden, W. D., *A.M.A. Arch. Surg.*, 1959, **79**, 385.
[10] McLachlin, A. D., ibid., 1959, **79**, 393.
[11] Dukes, C. E., *Dis. Colon. Rect.*, 1958, **1**, 413.
[12] Veale, A. M. O., *Nature (Lond.)*, 1958, **182**, 409.

Many cases, however, are the children of parents similarly affected, and here, knowing the risk, the clinician has scope for early prophylactic treatment. For example, in the largest series of families reported with familial intestinal polyposis, that of C. E. Dukes[2] from St. Mark's Hospital, in 13 of 33 families the mutant gene had affected three or more generations of a family. Similarly, 10 of 23 families reported from the State of Michigan[3] affected three or more generations. In one of the families whose members had intestinal polyposis with epidermoid cysts, fibromata, and osteomata, 15 individuals in four generations were affected.[4]

Prophylactic surgery is not needed in Peutz's syndrome, in which the risk of carcinoma is not high.[5-7] But when the polyps are confined to the colon and rectum, as is the case with both forms of familial intestinal polyposis, total colectomy soon after the polyps are recognized is the correct treatment. This anticipates the development of cancer. The only point at issue is whether all the rectum should be removed and the patient left with an ileostomy, or whether the lower rectum should be kept and the ileum anastomosed to the stump of the rectum, after any polyps in the latter have been removed.[8-11] There are obvious advantages in the latter procedure, if the number of rectal polyps does not make it impracticable; but there is the risk of malignant change developing in the rectal stump, and so this treatment should not be given where it is not possible to continue to keep the patient under supervision for the rest of his life.

While polyposis may develop as early as the age of 2, carcinoma is very seldom recorded before the teens (only one patient in 91 dying from cancer of the colon before the age of 10 in the St. Mark's Hospital and Michigan series combined[3]), and so it is reasonable to start the routine examination of the children of affected individuals at about the age of 10. This should be repeated about every two or three years, and the majority of those who have inherited the gene will have developed polyposis by the age of 20. These examinations should, Dukes considers, be continued at about five-yearly intervals at least until the age of 40,[11] by which age it is probable, but not certain, that those still without polyps have not inherited the gene. As a piece of practical eugenics, those affected should be told as young adults of the risk to their children, so that they may decide for themselves whether to have children or not.

It would obviously be helpful if there were some way by which the children who have or have not inherited the gene could be distinguished before the development of polyposis. In the families in which neoplasia of skin and connective tissue occur, these will serve as useful pointers, since the tumours are usually present from early childhood. In the uncomplicated cases of familial intestinal polyposis, it would be useful to have a marker gene on the same chromosome as, and close to, the mutant gene responsible for the condition. In one large family from New Zealand, in which probably no fewer than six generations are involved, a preliminary report indicates a linkage with the genes determining the MN blood types.[12] If this is confirmed it will be fortunate, since by testing for the Ss antigens as well, four varieties of the chromosome may be recognized, of which only NS is uncommon, and in many instances it will be possible to recognize soon after birth those patients who have inherited the gene for intestinal polyposis by determining the MNSs blood type.

RHEUMATOID NEUROPATHY

Though the aetiology of rheumatoid arthritis remains stubbornly hidden from us at the present time, nevertheless the increasing amount of attention being paid to this disease is producing valuable information which can often have immediate and practical clinical application. In 1957 F. Dudley Hart, J. R. Golding, and D. H. Mackenzie[1] reported a study of 10 patients with rheumatoid arthritis who had developed a peripheral neuritis, and a year later R. M. Mason and V. L. Steinberg[2] described a further six cases of a similar nature. While a number of studies had been done on the histology of peripheral nerves and small blood vessels in rheumatoid arthritis during previous years, clinical reports describing peripheral neuritis were almost entirely lacking before this apart from two accounts in the last century.[3 4] Since 1957 some 38 further cases have been reported in the European and American literature, and on pages 1594 and 1600 of the *Journal* this week Drs. Dudley Hart and Golding add to these a further 42 cases, and Dr. Steinberg another 18—a total of 60 additional cases. As a result, the clinical features of this syndrome seem to be clearly established.

The syndrome is seen in men with rheumatoid arthritis at least as frequently as in women. Patients usually have active severe disease associated with nodules, often with arteritic changes in the hands or feet, and a strongly positive test for the rheumatoid serum factor. Usually, but not invariably, these patients will be on corticosteroid therapy, probably in high dosage, and this may recently have been altered for one reason or another, or abruptly discontinued. Sensory symptoms predominate with numbness, paraesthesiae, or hyperaesthesiae, affecting the feet rather than the hands; all types of sensation are lost, often with the

[1] Hart, F. D., Golding, J. R., and Mackenzie, D. H., *Ann. rheum. Dis.*, 1957, **16**, 471.
[2] Mason, R. M., and Steinberg, V. L., *Ann. phys. Med.*, 1958, **4**, 265.
[3] Pitres, A., and Vaillard, L., *Rev. Médecine*, 1887, **7**, 456.
[4] Bannatyne, G. A., *Rheumatoid Arthritis*, 2nd ed., 1898. Wright, Bristol.
[5] Pepys, S., *Diary*, 1662 (August 31).

exception of position sense. The loss is of stocking or glove distribution, tending to be symmetrical but occasionally occurring as a mono-neuritis in the lateral popliteal or ulnar regions. Occasionally a median neuritis may suggest a carpal tunnel syndrome. Later motor weakness—usually foot drop—may follow in severe cases, but even with this development tendon reflexes may be retained. The prognosis is bad. Of Hart's 25 personal cases four died (16%), and five of Steinberg's series of 18 (28%) were dead within one year. The cause of death varies, but cardiac failure, especially from coronary thrombosis, predominates. The clinical course in the survivors is very variable and unpredictable, though motor weakness is a bad sign and there is so far no suggestion that any treatment influences it favourably. The best advice at present is that if the patient is on corticosteroid therapy the dose should be kept constant and the temptation to alter the dose (upwards or downwards) in an effort to "do something" should be resisted, except perhaps when the patient is obviously suffering from severe hypercortisonism; even then changes in dose should be very gradual and cautious.

Necropsy studies have usually revealed evidence of a generalized arteritis with damage to the vasa nervorum, and it is tempting to accept the view that it is this which accounts for the neuropathy. But this is not an invariable finding, and comparison with polyarteritis nodosa, in which an arteritis is the cause of peripheral neuritis, does reveal certain differences to which Hart and Golding refer. Notable among them is asymmetrical damage to motor nerves in polyarteritis nodosa, which contrasts with the symmetrical damage to sensory nerves in rheumatoid neuropathy. And, as they also point out, it was at one time readily accepted that the neuritis of diabetes mellitus was vascular in origin also—a view which is no longer tenable, though no alternative explanation has been found.

Clearly one important question arises: Is the apparent increase in the frequency of peripheral neuropathy in rheumatoid arthritis a real increase, and, if so, is it related to more frequent treatment with corticosteroids? Both series reported here contained examples of patients who had never been given these substances, so this is probably a feature of the disease itself. It may well be that many cases have been missed in the past—the symptoms of neuritis being misinterpreted as being due to the arthritis itself. This should no longer occur if this possibility is borne in mind, and if the other possible causes of these symptoms can be reasonably excluded—such as diabetes, subacute combined degeneration of the cord, chronic alcoholism, avitaminosis, malignant disease, amyloidosis, and pressure on nerve roots from various causes.

It seems likely, however, that excessive dosage, change of dose, or abrupt withdrawal of corticosteroids may precipitate or at least exacerbate the process, and this provides yet another reason for insisting that all alterations of dose of these substances should be under strict supervision. In severe cases with multiple rheumatoid nodules and a strongly positive test for the rheumatoid serum factor the risk that corticosteroid therapy may produce this complication must be weighed in the balance before a decision to begin it is made. In all such cases a full trial should be given to drugs not likely to be associated with neuropathy—aspirin, phenylbutazone, or gold, for example—before running the risk of being faced by the very distressing picture of an arthritic Mrs. Bennett so aptly quoted by Drs. Hart and Golding from *Pride and Prejudice*, and of having to reply like Samuel Pepys, "God preserve us! For all these things bode very ill."[5]

INCIDENCE OF PEPTIC ULCERS IN BRITAIN

One of the few established facts relating to the aetiology of gastric and duodenal ulcers is that the incidence varies in different communities and at different times. It is therefore reasonable to believe that environmental factors are important in their production and that a close study of the conditions under which the diseases become more or less frequent might give a clue to their cause. Many investigators have followed this path; but their conclusions have often been disputable, because their diagnostic criteria have not been sufficiently uniform.

One way of overcoming this difficulty has been to study the incidence of acute perforated ulcers. This has the advantage that in areas where the medical services are adequately developed every case will come to medical attention and the diagnosis will be established with certainty—whatever the method of treatment. Moreover, affected patients will not travel far for treatment, and it may be relatively easy to collect all the cases occurring in a particular population by studying a small number of institutions. With this technique B. Bager[1] in Sweden and C. F. W. Illingworth and colleagues[2] in Glasgow established that there had been an increase in the incidence of perforations and that this increase had exclusively affected duodenal ulcers. The technique, however, has the disadvantage that a difference in the incidence of perforations may reflect a difference in the liability of an ulcer to perforate rather than a difference in the incidence of the underlying conditions.

Examination of necropsy material eliminates this difficulty. But, unless a high proportion of deaths occur in hospital and a high proportion of subjects come to necropsy, it is hardly possible to know whether the results obtained are representative of the population at large. The best necropsy index is, probably, the incidence of ulcers in patients dying of other conditions—that is, all subjects being excluded in whom the ulcer was the cause of death. Using this index, G. Watkinson[3] showed that duodenal ulcers were found more often in the North of England than in the South, whereas the incidence of gastric ulcers was practically the same in both areas. Watkinson[4] also showed that

[1] Bager, B., *Acta chir. scand.*, 1929, **64**, suppl. 11.
[2] Illingworth, C. F. W., Scott, L. D. W., and Jamieson, R. A., *Brit. med. J.*, 1944, **2**, 617 and 655.
[3] Watkinson, G., *Schweiz. Z. allg. Path.*, 1958, **21**, 405.
[4] ——, *Gut*, 1960, **1**, 14.
[5] Pulvertaft, C. N., *Brit. J. prev. soc. Med.*, 1959, **13**, 131.
[6] Registrar General, 1958, *Decennial Supplement England and Wales, 1951, Occupational Mortality*, Part II, London.
[7] Doll, R., Jones, F. A., and Buckatzsch, M. M., 1951, *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 276, H.M.S.O., London.

the incidence of duodenal ulcers found by a department where there was a specialized interest in the stomach and duodenum was higher than elsewhere; so it is evident that necropsy data are, in this respect, subject to a substantial observer error.

No one method of estimating the ulcer incidence can provide a satisfactory estimate free from all objections; firm conclusions can be reached only by concerting the results of different studies carried out by different methods. C. N. Pulvertaft's study[5] of the incidence of peptic ulcer in York and the surrounding countryside is therefore of particular interest, as his data are derived from clinical diagnoses. The populations of York and of a rural area on three sides of the city are served exclusively by the local city and county hospitals, and nearly every fresh ulcer is diagnosed at one or other hospital. Cases first diagnosed elsewhere—for example, on holiday abroad—would also be recorded through the co-operation of local consultants and general practitioners, and it seems likely that Pulvertaft's figures provide a good estimate of the frequency with which fresh ulcers are diagnosed. A positive diagnosis was made only if the ulcer was seen at laparotomy or gastroscopy, was demonstrated radiologically, or, if it had been suspected previously, was found at necropsy; ulcers found incidentally at necropsy were excluded. The estimates are therefore conservative and comparisons with other clinical series may be misleading. But comparisons can be made confidently between subgroups of the population studied.

Altogether during the years 1952–7 the annual incidence of duodenal ulcers among persons aged 15 years and over was 2.15 per 1,000 men and 0.62 per 1,000 women; the corresponding figures for gastric ulcers were 0.53 and 0.31 per 1,000. The general pattern of distribution of ulcers by sex and site is similar to that reported in other clinical series. Pulvertaft's data also provide confirmation for the belief that the incidence of both gastric and duodenal ulcers is higher in urban conditions than in rural. Among women the urban excess was small (duodenal ulcers 1.2 : 1 and gastric ulcers 1.5 : 1). Among men it was larger (duodenal ulcers 1.7 : 1 and gastric ulcers 2.3 : 1), and it is notable that the ratio for all duodenal ulcers was identical with that for perforated duodenal ulcers alone. It is therefore unreasonable to suppose that the higher urban incidence was artificial and due to the greater ease of access to hospital in towns. The data also agree with those obtained in the Registrar General's occupational mortality study[6] and in the survey reported by R. Doll and colleagues[7] in the south of England in showing that gastric ulcer is predominantly a disease of the semi-skilled and unskilled labourer. Duodenal ulcer is more evenly distributed among the social classes, but it was also somewhat commoner in the lower economic groups —an observation which weighs against the common belief that it is characteristically related to responsibility.

Comparison of the figures for perforations alone with those reported for other cities shows that the incidence in York was 15–20% lower than in Glasgow, and that the incidence of perforated duodenal ulcers was more than 50% lower than in Aberdeen, while perforated gastric ulcers were somewhat commoner. The explanation for these differences is unknown. Speculation has been inhibited in the past by a gnawing doubt about the validity of the available data. Such doubts are no longer justified.

MEDICAL MECHANICS AT LOUVAIN

How often, one may ask, is useful research held up, or even prevented altogether, because necessary apparatus cannot be got? How much time is wasted by experimentally minded clinicians and medical scientists in peddling their ideas before the scrutineers of research organizations, charitable trusts, and the like? Scrutiny is of course essential, but is our whole machinery for putting at the right moment the right tools in the right hands too cumbersome and creaky? Some would say emphatically it is.

At Louvain University in Belgium they have found a novel answer to this problem. This ancient Catholic university (founded in 1425), with its very large faculties of medicine and science, is in a phase of rapid expansion. Since 1950 the number of students there has risen from 7,500 to over 12,000: with this there is of course a heavy demand from the various departments for research and other specialized equipment. To meet the demand the university has established its own University Technical and Experimental Centre (U.T.E.C.), staffed by university engineers, where apparatus wanted by the departments and not readily available commercially can be designed, developed, and produced up to the highest industrial standards. U.T.E.C. is of course remarkably well placed to do this. It can call on the research experience of the whole university; if a chemical problem arises there is a chemist to answer it; if the advice of an electronics engineer, a metallurgist, or physiologist is wanted it can be speedily obtained, and so on. There are experienced administrators to look after the Centre's finances, and a whole faculty of lawyers to safeguard the patent rights of new inventions.

Some idea of the diversity of the equipment designed and made by U.T.E.C. can be gleaned from a bare catalogue of items shown to invited representatives of the *Journal* at the Centre this month. At the university library, with its 800,000 volumes, there is a "continuous belt" machine to speed the delivery of books from one floor to another. At the teaching hospital, apparatus from U.T.E.C. ranges from a palatial multiple-cabinet morgue, with powered lifting to assist the attendants and full refrigeration, and an electronic control system for the heating of the whole ten-acre hospital site, to highly mechanized stereotactic equipment for brain surgery and a room for cancer research with luxuriously precise control of temperature and humidity. (The temperature in this room, it was said, can be kept constant within one-tenth of a degree centigrade.) Other hospital equipment includes a specially designed bath for paralysed patients and an air-conditioning system for the operating theatres.

At the U.T.E.C. workshops themselves the anatomical specimens are specially notable, as befits a foundation which numbers Vesalius among its sons. Chief among these are the plastic skeletons cast from flexible moulds of human bones. Their construction is remarkably good and their accuracy sufficient for most undergraduate purposes; they are more than adequate for teaching medical auxiliaries. The bones are put up as articulated skeletons, mounted skulls with the bones separated, "half-sets" for students, and separately. It is hoped that samples will be on view at the summer meeting of the Anatomical Society of Great Britain which is being held this year at the Royal College of Surgeons on July 1 and 2. At the workshops they are also developing suitable processes for making soft-tissue specimens, and some of these muscle-and-nerve preparations seem very promising. Pathological, biological, and botanical specimens are embedded in clear plastics for museum purposes. Other apparatus includes electronic equipment for the continuous recording of blood pressure, Geiger counters, an E.C.G.-monitor for use during surgical operations, small climatic chambers for the study of tropical plant physiology, and tilting, stainless-steel operating tables for rats and mice, tailored to the experimenter's requirements. This is just a sample of the activity that goes on.

The benefits to Louvain University—and to the outside research units, hospitals, and commercial firms who on occasion go to U.T.E.C. for equipment—are definite enough. The dangers of such a set-up are, on the one hand, that the unit may get bogged down by large routine jobs of little intrinsic research merit, though at Louvain the U.T.E.C. directors seem well alive to this: and, on the other, that the natural inventiveness of designers may progress too far in the direction of push-button machines for every occasion.

ULNAR NERVE LESIONS IN THE PALM

Wasting of the small muscles of the hand unaccompanied by sensory loss always raises the suspicion of motor-neurone disease. It is therefore as well to remember that lesions of the ulnar nerve in the palm of the hand can produce just such a picture. When the nerve is injured after curving round the pisiform bone, it has already given off its sensory branch to the palmar aspect of the ulnar two fingers, and usually its supply to the hypothenar muscles also. The result is thus a purely motor loss affecting the interrossei, the medial two lumbricals, and the adductor pollicis muscle. If the lesion is a little more proximal, the hypothenar muscles are also affected without sensory loss.

This syndrome was originally described by Ramsay Hunt,[1] and similar cases were reported by W. Ritchie Russell and C. W. M. Whitty.[2] More recently P. Ebeling and colleagues[3] have discussed a further nine cases and have shown that measurement of nerve conduction can be a useful aid to diagnosis. Not only can this procedure suggest a local nerve lesion, but it can sometimes indicate its site with some accuracy, and further help in assessing the beginning of recovery before clinical evidence is available. The cause of these lesions is almost always traumatic, and this can usually be discovered in the history. Sometimes the amount of trauma may be slight, because there is some source of internal pressure on the nerve. H. J. Seddon[4] described cases in which a palmar ganglion caused compression of the nerve, and similar lesions were found in four of Ebeling's patients. In such cases operation may hasten recovery, though recovery often occurs simply from protecting the nerve from further external pressure with a properly placed foam-rubber pad in the glove. Careful serial studies of nerve conduction may also help to establish the need for operation. It is important to bear in mind this diagnosis, which is a neat vignette of applied anatomy, and not to condemn the patient unnecessarily to the gloomy diagnosis of motor-neurone disease.

[1] Hunt, J. Ramsay, *J. nerv. ment. Dis.*, 1908, **35**, 673.
[2] Russell, W. R., and Whitty, C. W. M., *Lancet*, 1947, **1**, 828.
[3] Ebeling, P., Gilliat, R. W., and Thomas, P. K., *J. Neurol. Neurosurg. Psychiat.*, 1960, **23**, 1.
[4] Seddon, H. J., *J. Bone Jt Surg.*, 1952, **34B**, 386.

PREVENTION OF INJURY IN ROAD ACCIDENTS

Would improvements in the design of cars lessen the number of serious injuries arising from road accidents? Only research can provide the answer, and the Automobile Association has generously agreed to sponsor an investigation which, in the long run, should benefit the National Health Service by reducing the number of beds occupied by casualties from the roads. Announcing the plan after the annual meeting of the Automobile Association in London last week, the Duke of Edinburgh, who is President of the A.A. as well as of the B.M.A., said that a road injuries research group will work in conjunction with the Institute of Accident Surgery at the Birmingham Accident Hospital. One of the main objects of the group will be to find out the extent to which injuries are related to the design of vehicles, and the sum of £30,000 has been set aside to finance research on these lines for the next seven years.

Mr. W. Gissane, surgeon-in-chief at the Birmingham Accident Hospital, will supervise the research there. One of its purposes will be to compare engineers' reports on damage to vehicles with surgeons' reports on the injured, whether inside or outside the cars. Among the many points of design to be examined will be the steering assembly, which, as Mr. Gissane[1] says, can cause irreparable damage to vital organs. In his view the traditional design of the steering wheel is the most unnecessary single hazard in present-day car design. But brakes, headlamps, bodywork, tyres, and so on, will all be under close scrutiny in this research, which it is to be hoped the motor industry will wholeheartedly support.

The half-yearly indexes to Volume II of the *Journal* and *Supplement* for 1959 are now being despatched. Members who have not previously asked for the indexes to be sent regularly to them can obtain copies, post free, from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

[1] *Birmingham Post*, May 20.

Clinicopathological Conference

A CASE OF CARCINOMA OF THE BREAST

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This patient, a housewife aged 54, was admitted to Hammersmith Hospital in May, 1959, for pituitary ablation by radioactive implant to deal with her widespread breast carcinomatosis (Case No. 200,330; P.M. No. 8,823).

Clinical History

Professor T. RUSSELL FRASER: Her history contained no significant illness until 1957, when she noticed a lump in the left breast a few months after her periods had stopped. This was diagnosed as carcinoma. A radical mastectomy was performed, followed by deep *x*-ray treatment to all the local glandular areas. Thereafter she was well, or rather apparently well, until November, 1958, when after a trifling fall she fractured her left humerus. This was treated orthopaedically, and during the next month (December) she was given deep *x*-ray therapy to the area and testosterone injections. There was no evidence that any of her secondary deposits shrank in response to the testosterone, and, although there was temporary healing of the fractured left humerus, it refractured in February, 1959. In March she developed left sciatica and by April she also had a left foot drop, so she was given deep *x*-ray therapy to the sacrum and lumbar spine, which on *x*-ray examination had shown widespread deposits. Since that date she had also suffered from extreme weakness, nausea, and constipation and had become bed-ridden.

EXAMINATION AND INVESTIGATIONS

On admission on May 6, 1959, she was apyrexial, but wasted and pale and with her left arm in plaster. There was bilateral foot-drop and the ankle-jerks were absent. She showed extreme generalized muscular weakness. The right arm-jerks were just present, as also the knee-jerks. Her blood pressure was 190/80. On the left chest wall there were several cutaneous and subcutaneous nodules, apparently of carcinoma, and also radiodermatitis over the left shoulder and pectoral area, presumably as a result of her irradiation in 1957. Examination of her lungs revealed only crepitations at the right base. Nothing abnormal was felt in the abdomen and the liver was not enlarged.

Radiological examination showed widespread secondary deposits in her lumbar spine (Fig. 1), her pelvis, femur, and ribs. Radiographs of her hands showed no erosions, and those of her teeth showed a normal lamina dura. *Haematological examination:* Haemoglobin 8.4 g. (57%); W.B.C. 5,000 per c.mm., with 87% polymorphs and also several more primitive white cells and some nucleated reds suggesting a leucoerythroblastic anaemia. *Serum:* Sodium 133, potassium 2.3, chloride 95, calcium 9.2, phosphate 1.5, bicarbonate 27 mEq/litre; and proteins 6.6 (albumin 3.1) g/100 ml. Urea 86 mg./100 ml. Alkaline phosphatase 42 K.-A. units and tartrate labile acid phosphatase 0.9 K.-A. units/100 ml. *Urine calcium* 21.7 mEq or 434 mg. per 24 hours.

PROGRESS

Initially intravenous fluid and potassium supplements were given and restored her serum potassium, but she still remained very weak. Twelve days after admission, under general anaesthesia, 12 seeds of yttrium-90 were implanted in her pituitary by the pernasal route (Figs. 2 and 3) by Dr. Robert Morrison, but uraemia and drowsiness progressed, with persisting hypercalcaemia, and she died on May 21, 1959.

Clinical Diagnosis

1. Carcinoma of the breast with multiple bone secondaries.
2. Leucoerythroblastic anaemia.
3. Hypercalcaemia leading to uraemia.
4. ? Carcinomatous myopathy.

Post-mortem Findings

Dr. A. G. E. PEARSE: The post-mortem examination was carried out by Dr. P. Dawson 17 hours after death. The body was that of an elderly woman in a state of considerable emaciation. There was a scar of a left radical mastectomy and two nodules (secondary carcinoma) in the skin over the sternum. Metastases of

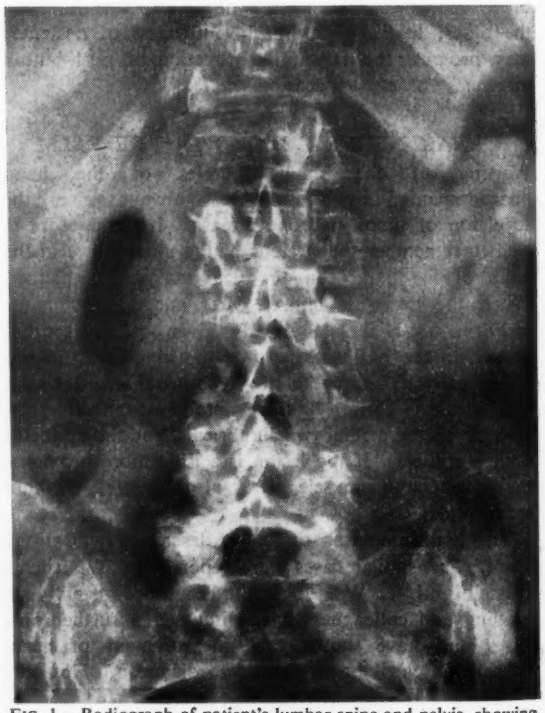

FIG. 1.—Radiograph of patient's lumbar spine and pelvis, showing widespread secondary deposits.

FIG. 2.—Yttrium seeds being implanted by needle pernasally.

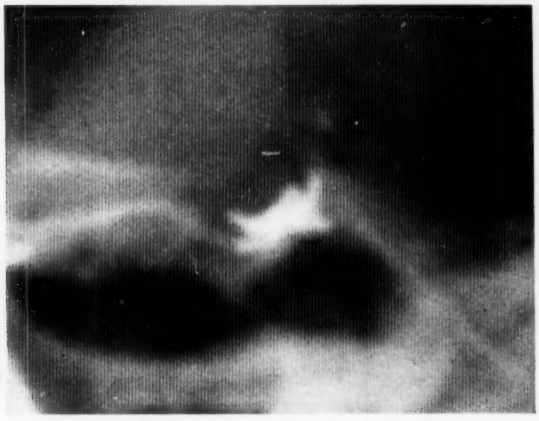

FIG. 3.—Final picture showing yttrium seeds in the lower half of the sella turcica to avoid damage to diaphragma.

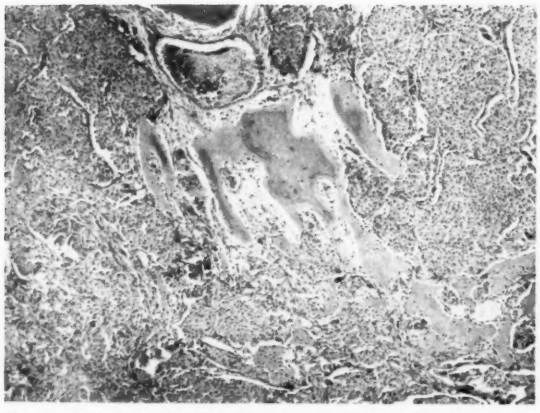

FIG. 4.—Secondary deposit of carcinoma of breast invading bone marrow. (×44.)

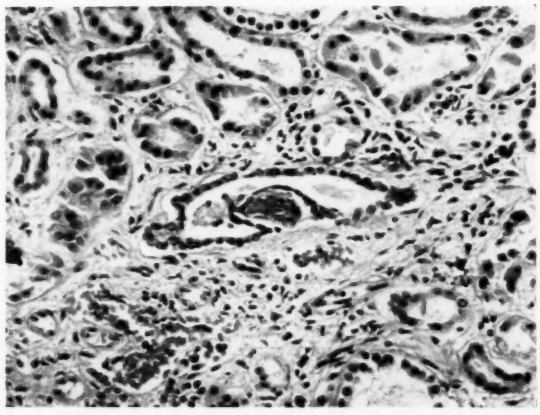

FIG. 5.—Section of kidney showing nephrocalcinosis. In the centre of the field is a dilated tubule showing a deposit of calcium phosphate lying immediately under the epithelium and bulging into the lumen. (×109.)

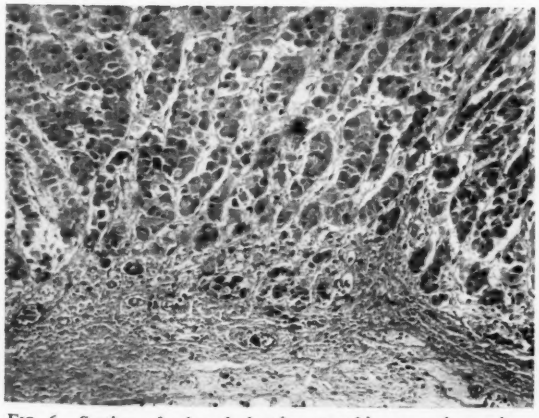

FIG. 6.—Section of adrenal showing atrophic zona glomerulosa and hyperplastic zona fasciculata composed of masses of large pink granular cells with complete absence of lipid storage. (×87.)

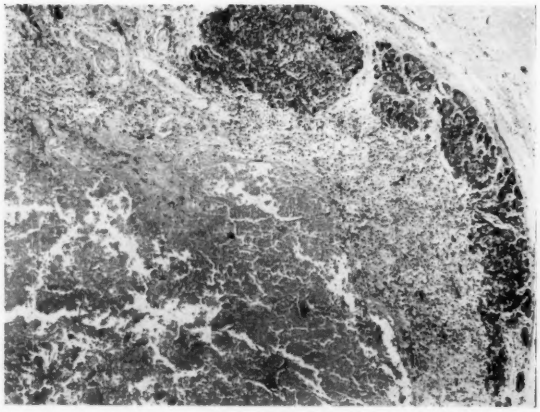

FIG. 7.—Section of one of the grossly enlarged parathyroid glands, showing extensive central necrosis with a thin surviving rim of active tissue. (×34.)

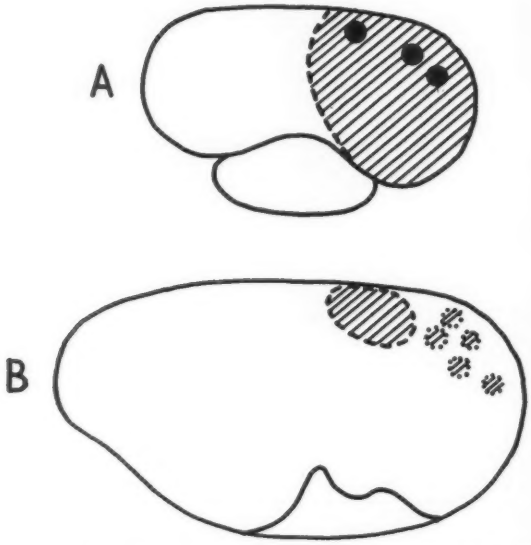

FIG. 8.—Diagrammatic representation of horizontal sections of the pituitary gland. A is 1 mm. from the inferior surface and shows the extent of necrosis (shaded) surrounding the yttrium needles (black). The smaller unshaded area is the pars nervosa, which was normal. B is a section through the middle of the gland. It shows the small degree of necrosis (shaded) at this level.

FIG. 9.—Part of the left lateral wing of the adenohypophysis showing numbers of greatly enlarged, fully granulated, acidophil cells. The smallest cell in the central group is a normal-sized acidophil. (×760.)

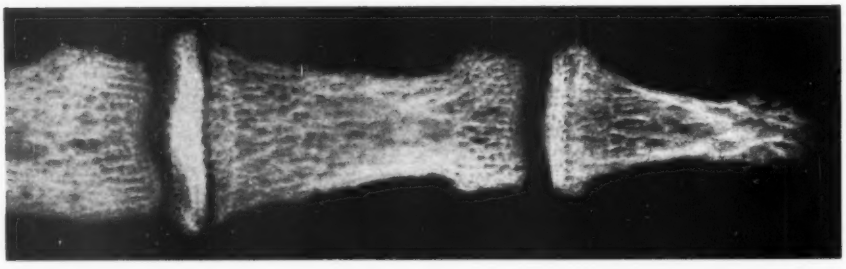

FIG. 10.—Radiograph of finger showing marked subperiosteal bone absorption of cortex in a patient with primary hyperparathyroidism.

FIG. 11.—Radiograph of skull in hyperparathyroidism showing bone absorption, giving a rather "woolly" appearance.

FIG. 12.—Radiograph of skull from same patient after removal of parathyroid tumour, showing complete reconstitution of the skeleton.

the poorly differentiated columnar-cell carcinoma of the breast were widespread. Except for the local extension (presumably from nodes in the left supraclavicular fossa) the most extensive spread was to the bone marrow (Fig. 4). Small secondaries were present in the liver, parietal pericardium, lungs, and right adrenal ; none were present in the brain, meninges, or spinal cord itself. Every vertebral body in the thoracic and lumbar regions contained tumour deposit, some being completely replaced by growth. The lowermost part of the cord and some of the roots of the cauda equina were compressed by the deformed vertebrae.

Kidneys : Weighed 315 g. together. Grossly, they appeared normal except for some streaking in the medullary rays. Microscopically there was diffuse nephrocalcinosis (Fig. 5), with deposits of calcium salts not only in the tubules and their walls but also in Bowman's capsule.

Thyroid was slightly enlarged, with a benign adenoma 1.5 cm. in diameter in the right lobe. Adrenals (12 g.) had pale cortices with patchy areas suggesting hyperplasia ; microscopically (Fig. 6) both showed diffuse cortical hyperplasia, especially in the zona fasciculata. The parathyroids were all enlarged, two being about three times and two about one and a half times the normal size. One contained a small oxyphil adenoma and another had a completely necrotic centre (Fig. 7). The other two showed diffuse hyperplasia with replacement of the normal clear cells with granulated cells and with large areas of protein secretions.

Pituitary : Nine yttrium seeds were lying on the right side of the cells outside the gland. Three were in the gland, and these were surrounded (as usual) by a zone of complete necrosis. Microscopically the whole of the lateral wing was affected in the lowest part of the gland, but at higher levels radiation damage was minimal (Fig. 8). The mucoid (basophil) cells were slightly overactive, but the clearest features microscopically (Fig. 9) were (1) hyperplasia of the acidophils and (2) large areas of chromophobe " adenosis." These latter may represent groups of degranulated acidophils. No damage to stalk or neurohypophysis was seen.

Pathologist's Diagnosis

1. Secondary carcinomatosis with leucoerythroblastic anaemia.

2. Nephrocalcinosis.

3. Acidophil hyperplasia of the pituitary with possibly consequent adrenal cortical hyperplasia. It is possible that the observed parathyroid hyperplasia was due to a pituitary cause also.

Discussion

Professor RUSSELL FRASER : There are several aspects of this patient which it might be interesting to discuss now. First, there is the question of what happened in the kidneys and why she developed renal leaks for potassium and phosphorus (among other substances), and why she went into uraemia. And there is the problem of why her parathyroids, if not other glands, were overactive ; and perhaps the question of the extent of the pituitary destruction which may have been achieved through implanting yttrium.

URAEMIA AND POTASSIUM LOSS

First the kidneys. I think the renal function picture we saw here is what we expect in severe hypercalcaemia from any cause ; the history suggests that this patient had it for a short period of time of at most weeks. The histology doesn't suggest that there was any other cause of uraemia than the hypercalcaemia. Perhaps Dr. Milne will shortly tell us why hypercalcaemia leads to a steady development of uraemia with renal tubular damage manifested by renal leaks for phosphorus, potassium, and other substances. In some of our other hypercalcaemic patients, as with this one, our first problem has been to treat the potassium deficiency and the uraemia. Perhaps after such emergency treatment the best way of treating the patients is to cause the serum calcium to return to normal, which is what we tried to do in this patient.

PARATHYROID OVERACTIVITY

Next I would like just to make a few comments about the parathyroids. For the clinician I don't think there is any doubt that our therapeutic decision was the right one—to attack the carcinoma if we could, irrespective of whether she had hyperparathyroidism as well. Now, on reviewing the problem, we must consider whether the parathyroid overactivity which Dr. Pearse has shown us could be regarded as secondary to any of her known diseases, such as either the kidney damage or the uraemia, or perhaps the carcinoma. I think we may say from her history that her uraemia couldn't have been longer than perhaps two weeks before she came here—that's perhaps three or four weeks before death. When she came here she had a blood urea of about 80 ; so this wasn't really very severe or very chronic uraemia, and therefore it seems hardly credible that the parathyroid hyperplasia could be due simply to the uraemia. That, of course, is a matter purely, I think, of how long she was in uraemia, and retrospectively we can only " guess-estimate " that. I don't think that we have any reason to think that the hyperplasia could have been a response to the widespread bone metastases. Therefore I am inclined to take the view (also, I think, Dr. Pearse's) that this is primary, not secondary, hyperplasia of the parathyroids. I don't think there is any way of telling, if I may say so, by pathological or histological criteria whether this hyperplasia was primary or secondary. It used to be claimed that this was possible, but I don't think pathologists now believe that.

YTTRIUM IMPLANT

Now perhaps the next point, on which I suppose we don't want to concentrate very extensively here, is the evidence of yttrium damage to the pituitary. The distribution of the seeds, if satisfactory, should lead to a functional deficit implying at least 85% ablation, else we would not be able to find the clinical or test signs of pituitary hypofunction usually obtainable in these cases. Well, of course, this is not a very suitable case for considering this issue, since she died at such an early stage—two or three days after the implantation, by which time she might have received a third of the radiation, but certainly not more and not its full effects. So while the effect seen represents a suboptimal radiation, only a later necropsy could have told us what destruction this implantation might have achieved.

This patient is especially interesting from the point of view of the diagnosis of hypercalcaemia and also the effects of hypercalcaemia on the kidneys.

BONE METASTASES AND SERUM CALCIUM

Professor J. MCMICHAEL : Is hypercalcaemia well recognized as a consequence of bone destruction in carcinoma ?

Professor RUSSELL FRASER: I think so, yes. It is largely a matter of how widespread the carcinoma is.

Professor MCMICHAEL: This was pretty widespread.

Professor RUSSELL FRASER: Yes. When you get a sufficiently widespread carcinoma, it is one of the recognized hazards. It is an important point, I think, to remember when one sees a patient with widespread bony carcinoma who is constipated, nauseated, and perhaps vomiting—a common explanation for which may be hypercalcaemia, but one which may not be thought of. Similarly, a very important clinical sign of this is a widespread peripheral vasodilatation, the normal

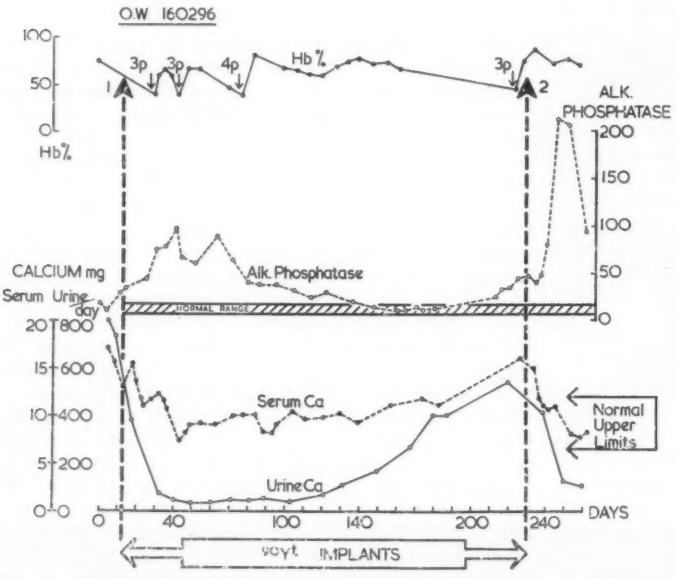

FIG. 13.—Serial data on case of hypercalcaemia due to widespread bony secondaries from carcinoma of the breast. Note initial high plasma calcium and normal alkaline phosphatase (measured in K.-A. units/100 ml.), and reversal of these levels after two pituitary implants to which the carcinoma responded.

accompaniment of extreme hypercalcaemia; and in these cases where these symptoms arise that clinical sign usually gives the hint.

WAS SERUM CALCIUM TOO HIGH?

A VISITOR: Is this level higher than would be usual even with extensive bone destruction?

Professor RUSSELL FRASER: We like to talk of grades in hypercalcaemia. The normal upper limit level of serum calcium is 5.5 mEq per litre, or 11 mg./100 ml. Above this we have a range of what might be called moderate hypercalcaemia up to about 16–17 mg./100 ml., or 8–8.5 mEq per litre, the level at which supersaturation with calcium and phosphorus begins. Above that level you enter the range of what sometimes is called "hyper-hypercalcaemia." That is the range in which the severe symptoms of vomiting and headache appear and where there is progressive damage in the kidneys, so that you have a vicious circle.

Professor MCMICHAEL: Have you seen this sort of level before?

Professor RUSSELL FRASER: Oh, yes.

Professor E. J. KING: But have you ever seen it so high in a case that didn't have a parathyroid involvement?

Professor RUSSELL FRASER: Yes, indeed.

Professor KING: Of that order?

Professor RUSSELL FRASER: Yes. I've got two slides in my pocket if you are really curious.

Professor MCMICHAEL: I think it would cheer Professor King to see them. It's an extraordinary high one.

Professor RUSSELL FRASER: I don't think the level is in any way related to the cause of the hypercalcaemia; it is rather a question of the severity of the cause. We have seen that level, of course, in hyperparathyroidism as well as in metastatic bone disease. The metastatic bone disease may often kill the patient by other means before you get it quite so severe. Also, once the patient gets into this "hyper-hypercalcaemic" state it is often either cure or death within a matter of weeks, so that we don't very often have the patients with us at that phase.

Now Fig. 13 shows the data of a patient who had the same primary disease and a similarly high level of serum calcium, 16–17 mg./100 ml. initially, before she had the yttrium implant; a high urinary calcium level is also shown. The other item on this chart to which I should like to draw your attention is the alkaline phosphatase. Before the yttrium implant, at the time when we saw the hypercalcaemia, the alkaline phosphatase level was normal. Following the yttrium implant there is a fall in the serum calcium and the urinary calcium and a rise in the alkaline phosphatase—the response to the treatment of the carcinoma stopping the excessive bone destruction and allowing new bone to form and recalcify. This particular patient had a second yttrium implant because the first one was incomplete by our hypopituitary test criteria. The first wasn't a complete hypophysectomy, but she did have a very good clinical response. When the hypercalcaemia recurred, owing to the carcinoma getting under way again, she had a second implant; after which the alkaline phosphatase again went up and the serum calcium went down. Now, incidentally, this patient is well, going to work, and she also has both clinical and test evidence of hypopituitarism. So that finally perhaps the pituitary destruction was complete.

Professor KING: Was the acid phosphatase up on that?

Professor RUSSELL FRASER: Yes. I haven't got the data here. That enzyme level followed what you might expect—along with minimal carcinoma growth it was low, and at the phase of maximal carcinoma growth it was raised. The next chart (Fig. 14) shows the data of a similar patient. Here we had initial serum calcium levels of the order of 9 mEq per litre and serum potassium levels near 2, along with low normal alkaline phosphatase levels.

CAUSE OF THE RENAL FAILURE

Professor MCMICHAEL: Dr. Milne, would you comment on the kidneys?

Dr. M. D. MILNE: *Only* on the kidneys, Sir?

Professor J. MCMICHAEL: Well, you know I never put the brakes on you.

Dr. MILNE: I feel rather diffident in talking at all here because some of my views I think are at variance, but I suppose it is more interesting if we don't all say the same thing. First of all the reason for renal failure in hypercalcaemia: a serum calcium of this quite astronomical level invariably, I think, does cause renal failure. Experimentally it seems to be due, not to the actual calcium deposited in the kidney, but to the reabsorption of calcium. The evidence for that is that a calciferol poisoned animal will have very severe renal deficiency. You can kill him, of course, and measure the calcium in his kidney. Alternatively you can allow him to recover and his renal function will slowly get back to normal; if you then kill him, he has still got the same amount of calcium in the kidney. The renal failure is not due to the actual nephrocalcinosis. That's an epiphenomenon of the hypercalcaemia. The temporary failure is due to some functional defect concerned with the reabsorption of calcium in the renal tubule. It seems to occur when there is excess passage of calcium across the renal cell.

BIOCHEMICAL UPSET

There are several points about the biochemistry. First of all there is a technical point. Professor Russell Fraser said some of us were not used to the phosphate in milliequivalents—I count myself in that ignorant group. There is, however, just a little technical point—to convert mEq/litre to mg. phosphate/100 ml. you said you would multiply the figure by 1.8—the actual sum is the atomic weight, 31, divided by 10 times that awful valency figure of 1.8, i.e., a physiological valency—a thing that pure scientists would not accept—which comes to 1.725. So the factor of 1.8 would give a little constant error in our figures.

Professor RUSSELL FRASER: May I interject that I am with you in the ignorant group that can't follow the milliequivalents for phosphate.

Dr. MILNE: Secondly, the alkaline phosphatase; well, this to me does not seen terribly puzzling. I think you can get two extremes in metastatic deposits of bone, although many individual exceptions may occur. Statistically, osteolytic deposits are associated with little rise of the alkaline phosphatase, whereas osteosclerotic deposits are accompanied by considerable rise. In multiple myelomatosis, which is the classical extreme of purely osteolytic deposits, the alkaline phosphatase is rarely raised and this is very useful in differential diagnosis. Very occasionally, however, even in this type of bone neoplasm, it may be raised. At the other extreme, in secondary carcinoma from a primary neoplasm of the prostate, which is typically osteosclerotic, the alkaline phosphatase is, I think, almost constantly raised. Carcinoma of the breast is one where there is an intermediate picture. Obviously on her *x*-ray the process looks chiefly osteolytic, but I think if sections of bone had been done in detail there would have been osteoblastic areas. I would have thought that a raised alkaline phosphatase is quite common in secondary carcinoma, without bringing in the liver, which was obviously virtually normal.

I think there is a double explanation for the serum potassium. Quite clearly there was a renal potassium leak. There was a daily loss of more than 30 mEq of potassium despite a grossly low serum potassium. This, however, is not uncommon in the nephrocalcinotic kidney, whatever the cause. It can occur in primary hyperparathyroidism, in calciferol poisoning, and in secondary neoplasia of bone with osteolysis. In addition there was considerable vomiting with loss of potassium in the vomit.

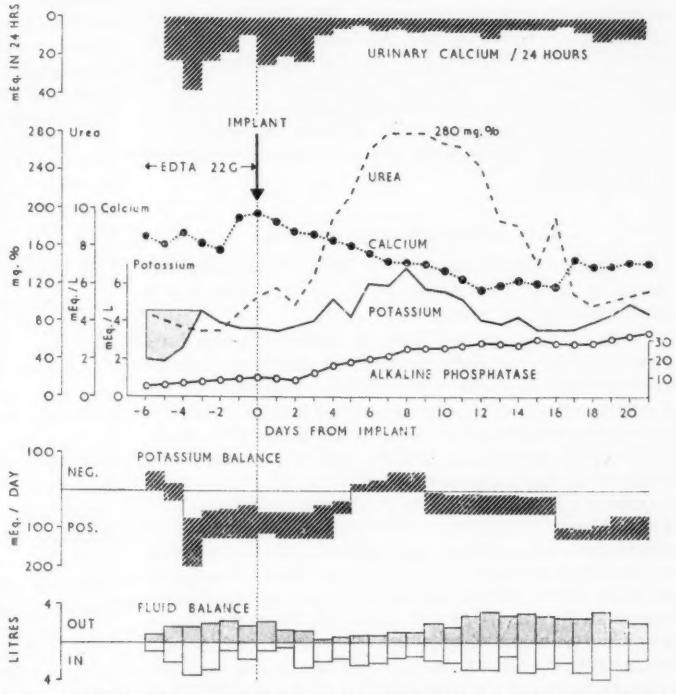

FIG. 14.—Serial data on another case of carcinoma of breast with hypercalcaemia before and after yttrium implant.

The one puzzling feature, I think, is this low serum phosphate. Now, obviously, the facile way to account for this would be to say: "Oh, yes, hyperparathyroidism." But at these levels of serum calcium the blood is supersaturated and there is always ectopic deposition occurring. I would like to ask if it is quite certain that the calcium–phosphorus ratio in this deposited ectopic calcification is exactly the same as the fairly constant calcium: phosphorus ratio in bone. Obviously, if there was a greater proportion of phosphate in calcium laid down ectopically, this would tend to cause an artificial lowering of phosphate in relation to calcium, because there would be more phosphate laid down per unit of calcium than is reabsorbed from the bone.

PARATHYROID HYPERTROPHY

The other point is the hyperplasia of the parathyroids. This we have been told in the opinion of the presenter

is "primary." Well, this to me seems a very odd coincidence. Hypertrophy of the parathyroids is a very common accompaniment of the type of bone neoplasia which most constantly causes hypercalcaemia, i.e., multiple myeloma. In many cases of multiple myeloma with hypercalcaemia one gets hypertrophy of all the parathyroid glands, as in this case. I don't mind coincidence once, but many coincidences I dismiss, and therefore I think this is *secondary* hyperparathyroidism. But I find this difficult to explain on current concepts because the usual facile explanation of the cause of secondary hyperparathyroidism is chronic hypocalcaemia. This explains the secondary hyperparathyroidism of renal disease and the secondary hyperparathyroidism of long-standing osteomalacia, but it does not explain the parathyroid hypertrophy which is a very common accompaniment in hypercalcaemia from bone neoplasia, particularly from myelomatous deposits in the skeleton.

LEUCOERYTHROBLASTIC ANAEMIA

Professor J. MCMICHAEL: Dr. Milne always explains things so well. Professor Dacie, this patient had a leucoerythroblastic anaemia. . . .

Professor J. V. DACIE: This, of course, is a side issue in this patient, but she had a severe anaemia. Leucoerythroblastic anaemia is an anaemia characterized by small numbers of nucleated red cells and primitive leucocytes, usually myelocytes, in the peripheral blood. The blood picture is usually quite distinct from leukaemia. It is associated with invasion of the bone marrow by tumour and it is sometimes in fact an early sign of this occurrence. The cause is a matter of speculation. Most people have thought that the presence of nucleated red cells and myelocytes in the peripheral blood is due to their being derived from extramedullary foci, and the fact is that if you look for them microscopically you can usually find these foci, particularly in the spleen. The anaemia is apparently due not only to replacement of the bone-marrow by tumour but also to increased haemolysis, and if you look at blood films you find that the red cells vary considerably in size and shape. Clearly, the actual formation of the red cells has been harmfully affected in some way by the presence of the tumour in the bone-marrow, and this is probably responsible for the diminished red-cell life.

CALCIUM IONS

Dr. I. DONIACH: Could I come back to the parathyroids for a moment and ask Dr. Milne a question? I think, in the explanation given of parathyroid hyperplasia in response to kidney disease and so on, it is said that it results from a fall in blood level of ionized calcium. Now in your examples of raised calcium in multiple myeloma is there a rise in the blood level of ionized calcium?

Dr. MILNE: Well, I would have thought certainly, because if these lesions produce that "awful awful" disease of "hyper hyper hyper" hypercalcaemia with neuromuscular symptoms and cause severe vomiting, then the ionized calcium is at fault. One would not get any symptoms if the calcium was either protein-bound and/or chelated. So I think, even without measuring it, you can be certain that at a level of calcium of 18, causing neuromuscular symptoms of this degree, there is an increase in ionized calcium.

Professor KING: That is borne out by the deposition of calcium. This sort of salt-bound calcium must be calcium iodide.

RADIOLOGICAL SIGNS OF HYPERPARATHYROIDISM

Dr. R. STEINER: When hyperparathyroidism was suspected, we looked very carefully for bone changes and found none. Their appearance must be a matter of time, I should think; they take quite a long time to develop. The sort of thing one ought to see is the cortical bone absorption which Professor Fraser has already mentioned. On this radiograph of a finger (Fig. 10) you can see very beautifully this very marked subperiosteal absorption of cortex in a patient with primary hyperparathyroidism; you get the same effect, of course, in secondary hyperparathyroidism. We looked for this sign very carefully and found no evidence of it. Another sign is the bone absorption we see in the skull and in the flat bones, giving a rather "woolly" appearance (Fig. 11). Compare this with the next radiograph (Fig. 12) of the same patient, taken after the parathyroid tumour had been removed, in which you can see a complete reconstitution of the skeleton. The last sign is cystic change. In primary hyperparathyroidism you may see a big bone cyst in a rather thin and demineralized bone, but again in the patient under discussion we found no evidence of this. Radiologically there was not the slightest sign of excessive parathyroid activity, and I would like to ask Dr. Pearse if there was any histological evidence of massive osteoclastic activity and osteitis fibrosa?

Dr. PEARSE: You mean formation of new bone? As Professor Harrison points out, the presence of woven bone in the picture which I showed you, and indeed elsewhere in other sections, indicates that new bone was being laid down.

Dr. STEINER: Could it be carcinoma in those sections?

Dr. PEARSE: Yes, it could. This answers actually, I think, Dr. Milne's question about the phosphate—there is definitely new bone formation going on, although the overall effect is still osteolytic. I would like to defend a little "my" theory about it being "primary" hyperparathyroidism. Nothing is ever primary so far as I am concerned, and what I would like to suggest, although there is no absolute evidence for it, is that it was secondary to pituitary activity. There is no pituitary hormone which is supposed to maintain the parathyroid, but there will be; there certainly are several which maintain the adrenal cortex. Something was maintaining the adrenal cortex in the state in which we found it, and there was hyperactivity of the cells which are most likely to maintain the parathyroid, i.e., the acidophils. So I regard the hyperparathyroidism as "primary" if you like, but, really, as secondary to the pituitary hyperactivity rather than secondary to the hypercalcaemia or to anything else like that. I should like to say also that in experimental damage to the kidney produced with calciferol, in animals, the damage to the tubular mitochondria is enormous. If there were similar damage here, again, the dysfunction would be enormous.

NEUROMUSCULAR WEAKNESS

Dr. C. PALLIS: It was suggested that her muscular weakness might have been due to carcinomatous neuromyopathy. Carcinoma of the breast is a very rare cause

of this moderately rare condition, but was reported, I believe, in the recent review by Brain and Henson.* In this case, in a context of general weakness, there seems to have been, in addition, gross focal weakness and atrophy affecting the legs and buttocks. There was a history of sciatic pain followed by foot-drop, and both ankle jerks were absent. In the presence of multiple metastases in the lumbar vertebrae, involvement of the roots of the cauda equina seems a much more likely explanation.

Professor MCMICHAEL: I suppose we could account for the muscular weakness on the extreme disturbance of the electrolytes.

Professor RUSSELL FRASER: Yes. I think the idea that it depended only on serum potassium has been eliminated, but hypercalcaemia itself is a great cause of neuromuscular weakness and I think perhaps that may have been the major factor.

Professor C. V. HARRISON: I think we could decide whether there was parathyroid hyperactivity—I don't mean at this moment, but I think we could tell by examining the sections of this patient's cancellous bone in sites clearly free of tumour. You would get osteoclastic resorption with marrow fibrosis in an area where the presence of tumour could not explain it. I don't suppose that has been done, because we were looking for tumour, but I think we could do it now.

*Brain, R., and Henson, R. A., *Lancet*, 1958, **2**, 971.

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Drug Treatment of Disease

BACILLARY DYSENTERY*

BY

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The bacillary dysenteries (shigelloses) are of world-wide distribution, but are particularly prevalent in warm countries where sanitation is defective. In Great Britain they are apt to occur epidemically in institutions, especially those for children or for mental patients. The organisms responsible are species of the genus *Shigella*; they include *Sh. shigae, Sh. schmitzii, Sh. flexneri, Sh. boydii,* and *Sh. sonnei.* There are several types and variants of *Sh. flexneri* and also *Sh. boydii.* The first to be identified, *Sh. shigae,* is the most virulent of these organisms and is more particularly found in the tropics; *Sh. sonnei,* the least virulent and one which rarely causes death, is that usually found in Britain. To an increasing extent *Sh. sonnei* is becoming the predominant species throughout Europe and the Middle East.

Sulphonamides

During the first world war, when there was no specific treatment for them, the bacillary dysenteries caused great morbidity and a considerable mortality in the forces, notably among those engaged in the Eastern Mediterranean theatres of war. At the beginning of the second world war sulphaguanidine, a sulphonamide which in passing through the bowel is but little absorbed, was shown to arrest clinical attacks of Flexner dysentery in children in a dramatic manner. It proved of equal value in adults serving in the forces in the Eastern Mediterranean; therefore it was produced on a large scale for the treatment of bacillary dysentery among the British forces wherever the disease was prevalent. As a result bacillary dysentery ceased to be a continuous major problem in the maintenance of operational activity by the troops.

While the drug initially was still in short supply some patients suffering from bacillary dysentery were treated with the freely absorbable sulphonamide sulphapyridine. This proved effective in controlling the dysenteric attacks but was prone to cause crystalluria, leading to anuria which, if not relieved, proved fatal. This hazard is particularly great in a patient suffering from a febrile and dehydrating disease, associated as this is with vomiting, diarrhoea, and sweating, in a hot climate. Consequently sulphaguanidine, to the exclusion of other sulphonamides, was adopted by the British forces for the treatment of bacillary dysentery. The American forces, when later engaged, preferred the freely absorbable sulphadiazine as their choice; when using it certain recommendations were laid down for the prevention of crystalluria, including dosage with alkalis to render the urine alkaline. The latter may not be possible even when the effort to achieve it is pushed to the stage of alkalosis.

Drug Resistance

After the sulphonamides had been in use for a few years, drug-resistance became evident during an outbreak of Flexner bacillary dysentery in children in an institution; sulphonamide treatment in the earlier cases proved effective, while in the later cases it failed to control the infection. The acquirement of drug-fastness by strains of *Shigella* is now a recognized risk attending their treatment with the sulphonamides.

Antibiotics

These sulphonamide-resistant infections were treated with streptomycin, given orally; it proved therapeutically active, though less so than had the sulphonamides in the earlier cases. Streptomycin when given orally is poorly absorbed; it therefore does not produce the toxic side-effects with which its parenteral administration is associated. It is not inactivated materially in the intestine. Other antibiotics, especially chloramphenicol and the tetracyclines, have since usually proved to be more efficient than is streptomycin for the treatment of shigellosis. Drug-resistance to the sulphonamides is

*The article by Dr. Adams on "Amoebiasis and Amoebic Dysentery" in this series appeared in the *British Medical Journal* of March 26 (p. 956).

especially likely to be acquired by strains of *Sh. flexneri*; *Sh. sonnei* infections often do not respond to sulphonamide treatment, or, if they do so, very rapidly become resistant to it. Therefore in these infections, and especially the latter, antibiotic therapy is the treatment of choice on all occasions whether or not sulphonamides also are given. So far there has been no evidence of the development by strains of *Shigella* of drug-fastness to the wide-spectrum antibiotics.

DRUG THERAPY IN PRACTICE

Sulphonamides

Where cost and availability are of significance, as in the tropics, sulphaguanidine and the later drugs of the same type (succinylsulphathiazole, phthalylsulphathiazole) still are widely and effectively used for the treatment of the forms of bacillary dysentery amenable to them. The dosage advocated is about 0.1 g. per kg. of body weight by mouth initially; half this dose is given 4-hourly thereafter until at least 24 hours after the diarrhoea ceases. This same dose is then continued at 8-hourly intervals for at least another three days. Ten days is the maximum period over which these drugs should be given. In practice, if they are effective the result of treatment should be clearly evident within 48 hours of its start. In round figures the dosage for an adult with any of these three drugs is initially 6 g. orally, followed by half this amount at the appropriate intervals.

Other sulphonamides, particularly sulphadiazine, are equally effective; but their use is governed by the considerations to which reference has been made. In tropical practice, especially up-country, most British workers adhere to the view that they are better avoided if the less readily absorbable compounds are available.

Antibiotics

Where cost and availability are not of prime importance the broad-spectrum antibiotics, in the form of chloramphenicol or the tetracyclines, by mouth are the first choice. The tetracyclines are not so rapidly absorbed from the intestine nor so freely diffused as is chloramphenicol. The larger the oral dose the less, proportionately, are the tetracyclines absorbed from the bowel and the greater, therefore, is the concentration of these drugs in the stools. In bacillary dysentery, unlike typhoid, the causative organisms are localized in the gut; so this may be an advantage in the treatment of this condition if the causation is beyond doubt and is not complicated by the incidence—for example, during an epidemic in children—of cases of gastro-enteritis due to infection with *Salmonella* or coliform organisms.

Chloramphenicol generally is claimed to be more effective than are the tetracyclines. It can be given orally to infants or children at a daily dosage of 50 to 100 mg. per kg. body weight, in divided doses, for five days. Adults can be given 3 to 4 g. daily, by mouth in four divided doses, for the same period. It is effective against most strains of all species of *Shigella*, and these develop no acquired resistance to it. Adults suffering from sulphonamide-resistant Shiga or Flexner dysentery have responded rapidly to an initial dosage of 2 g. followed by 1 g. in 12 hours and again in 24 hours. Toxic side-effects in the form of stomatitis and glossitis, diarrhoea, and pruritus are less than those associated with tetracycline treatment. Chloramphenicol may depress the bone marrow. Allergic skin manifestations, which may occur in a few sensitive patients, clear on stopping the drug.

A dosage scale of oxytetracycline ("terramycin") found satisfactory in one considerable epidemic was as follows: for children of 6 months or less, 25 to 50 mg.: up to 1 year, 100 mg.; from 2 to 5 years, 150 to 200 mg.; older, 250 mg.; and adults, 250–500 mg. These amounts were given daily by mouth, in divided dosage, for five days. Bigger daily doses than these have been given over longer periods without ill effect.

Sulphonamide-resistant strains of Shiga and of Flexner dysentery in adults responded readily to dosage initially of 2 g. and then 1 g. at 12 hours and 24 hours. Chlortetracycline ("aureomycin") produced a similar result in this group of patients.

The toxic side-effects of tetracycline treatment, though very rarely seen, are allergic and neurotoxic, nausea, and blood dyscrasia. In addition, treatment with this drug by depressing the normal bacterial flora permits overgrowth of *Candida albicans*; this may lead to stomatitis, glossitis and a hairy tongue, and pruritus ani and vulvae. Very rarely after prolonged dosage this overgrowth can assume alarming proportions, with grave infection of the alimentary, respiratory, and genital tracts. The development of resistance to tetracycline has not been found in strains of *Shigella*.

Streptomycin, if prescribed, is given orally in doses of 0.5 g. twice daily regardless of age. It is not absorbed to a material extent from the bowel; therefore there is very little risk of the development of its classical toxic side-effects; here also there is no evidence of acquired drug-resistance.

A combination of antibiotics and of sulphonamides, such as streptomycin and sulphaguanidine ("guanimycin"), is very effective in treating gastro-enteritis of infants. The dosage is 20 mg. per lb. (45 mg. per kg.) of body weight daily. "Streptotriad" (each tablet containing streptomycin 65 mg., sulphathiazole 100 mg., sulphadiazine 100 mg., and sulphamerazine 65 mg.), in a dosage of 3 tablets eight-hourly for six days gave good results in the treatment of shigellosis in Cyprus. Chloramphenicol with sulphaphthalidine in combination has also been used successfully; other combinations of antibiotics with soluble and insoluble sulphonamides have their advocates. These and similar combinations possibly lessen the risk of development of sulphonamide-resistant strains of *Shigella*.

In the most severe forms of infantile gastro-enteritis of African children, much of it due to *Shigella* infection, a combination of streptomycin (20 mg./kg.) and chloramphenicol (40 mg./kg.) orally proved very effective as a chemotherapeutic agent, when adequate steps were promptly taken to rectify loss of fluid and electrolytes owing to the disease.

Supportive Treatment

In fulminating attacks of bacillary dysentery, as in other grave infective disorders, early supportive treatment with corticosteroids or gamma-globulin may carry a patient on long enough for the specific treatment to control the infection, and thereby be a life-saving measure. In no way does such treatment replace the specific treatment; the latter must not be delayed when the former is employed.

Dehydration is an accompaniment of severe bacillary dysentery; it is of particularly serious import in children. Therefore in the treatment of children, when there is evidence of its need, fluid additional to the oral intake should immediately be given parenterally to remedy the deficit of fluid and salt, to offset the continuing loss of these, and to meet the child's normal requirements. The estimated daily requirement of a normal child under 6 months of age is 70 ml. of fluid per lb. body weight (150 ml./kg.); up to 1 year, 60 ml./lb. (125 ml./kg.) body weight. At 3 years a total of 1 to 1.5 litres a day is needed, at 8 years 1.5 to 2 litres, and over 10 years at least 2 litres daily. A child moderately dehydrated has lost 5%, a severely dehydrated child 10%, and a very gravely dehydrated child up to 20% of its body weight in fluid. Thus a severely dehydrated child weighing 9 kg., whose estimated normal weight is 10 kg. (22 lb.), requires prompt infusion of 1 litre of fluid to correct his existing deficit. Dehydration in children demands immediate and adequate remedy; of itself it is a major cause of infant death. As an emergency measure 600 ml. of fluid can safely be given subcutaneously to a clinically dehydrated child suffering from gastro-enteritis or dysentery when it is first seen.

Fluid, under suitable conditions, is best given by drip infusion intravenously; for a child it should be in the form of one-fifth to one-half strength normal (physiological) saline, or similar-strength compound sodium lactate injection (*B.P.* 1958) (Hartmann's solution), with 5% added dextrose in each case. The infantile kidney does not excrete salt as efficiently as does the adult; overloading of the child with salt must therefore be avoided; excessive infusion can likewise be disastrous. If intravenous treatment is not possible, these solutions can be infused subcutaneously with hyaluronidase. They also should be given orally, and are palatable to a child. The efficient re-establishment and maintenance of fluid and electrolyte balance in children are matters needing judgment and clinical experience, and it is not so amenable to control by laboratory estimations as it is in adults.

Complications

The common complications of bacillary dysentery are inflammatory lesions of certain organs, notably the eyes, joints, and peripheral nerves; they are attributed to absorption of the toxins. They can be forestalled by early specific treatment. If they do occur they subside under palliative treatment without permanent defect.

Prophylaxis

There is no vaccine or similar protective inoculation against infection. Under very special conditions over limited periods of risk sulphonamides have been given to afford protection against the disease; this practice is undesirable other than as a most exceptional measure.

The Biological Journal is to be published twice a year by the Biological Society of the University of St. Andrews, and is a successor to a magazine first published by the Society for its own members in 1952. It will present reports of recent research and articles of general interest on all aspects of biology for both amateur and professional. Individual copies cost 2s. 6d.; details may be obtained from *The Biological Journal*, 67, Arden Street, Edinburgh, 9, Scotland.

THE TREATMENT OF PSYCHOPATHS*

BY

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Psychopathy is so ill defined that it is essential, before considering treatment, to develop some clinical classification. The first part of this paper is directed to that end.

If we consider the three best-known definitions—those of Henderson (1939), East (1949), and the Mental Health Act (1959), we find four, and only four, common elements, which may be set out as follows:

	Excluding Clause	Time Factor	Description of Behaviour	Requiring Treatment
Henderson (1937)	Not amounting to mental defect	Throughout their lives or from a comparatively early age. Usually recurrent or episodic	Antisocial or asocial conduct	Social, penal, and medical
East (1949)	Non-insane, psychoneurotic or mentally defective	Persistently	Unable to adapt to social requirements on account of abnormal peculiarities of impulse, temperament, or character	Specialized medical and rehabilitative treatment instead of or in addition to ordinary methods of punishment
Mental Health Act, 1959	Whether or not including subnormality of intelligence (i.e., independent of sub-normality and mental illness)	Persistent	Abnormally aggressive or seriously irresponsible conduct	Requires or is susceptible to medical treatment

We are therefore justified in considering the psychopath as one who does not fit readily into other psychiatric categories, who is persistently antisocial or asocial, and who needs specialized treatment. As soon as we try to go further, in what can be observed now, in the past, or in matters of prognosis, we are in difficulties.

The follow-up studies of Gibbens *et al.* (1959) have shown prognosis, even in aggressive psychopaths, to be very uncertain, in respect not only of frequency but also of quality of offences.

To look back into the earlier history for confirmation of the diagnosis is even less reliable. "Even in childhood," writes Noyes (1939), "the future psychopath usually shows signs of unwholesome personality traits." But the behaviour traits which he then instances are so very common in the histories of those who are never considered psychopathic that we are not afforded much help.

Many attempts have been made to link psychopathy with coexisting specific personality qualities. There is the danger, however, that qualities common to a wide range of non-psychopathic individuals will take on a spuriously ominous meaning when observed in clinics, remand homes, or prisons, and that such backgrounds might be causing or uncovering the qualities. Quoting Noyes again, the psychopath "often conceals his own motives from himself by a superficial rationalization":

*Modified from a paper read to the Royal Medico-Psychological Association in October, 1959.

this surely might be observed in all of us. Other supposed qualities—for example, "a defect in keenness and delicacy of sentiment"—need no further comment. Even the well-known and oft-quoted qualities such as lack of real sincerity and co-operation in treatment (Cleckley, 1941), lack of anxiety and inability to feel guilt, no emotional feelings towards anyone (Bender, 1947), completely egocentric, hedonistic, opportunistic, unable to foresee consequences—all these are very suspect in that they can be observed only in some psychopaths and sometimes in non-psychopaths.

Examples could readily be quoted of persistent serious antisocial behaviour, not related to psychosis or mental deficiency, in which there is a high degree of anxiety and guilt, and a genuine wish for treatment. Lack of guilt, lack of caution or discretion, failure to reckon with consequences, are far more often seen in relation to the offence than as factors pervading the whole personality. "No emotional feelings towards anybody" implies a very rare state. This may be illustrated from experience in approved schools. It is known that a big proportion of chronic adult recidivists, whom most would agree to label psychopathic, have been through juvenile correctional establishments, so that a proportion of the inmates of these establishments must be psychopaths or embryo psychopaths. Yet when the population of an approved school is examined it is found not that the children are unable to make emotional contacts but that they are already so deeply involved in an unsatisfactory, disappointing, or conflictful relationship, usually with the parents, that it hinders them in their other relationships.

Nevertheless it is rare to find young offenders who cannot make a meaningful relationship either with a staff member who sets out to help or, in the very rebellious, with another handicapped or delinquent individual. It is particularly impressive to observe that, in such an institution, individuals who have been considered at staff conferences or in classifying procedures to be "completely egocentric" can suddenly (perhaps on coming into contact with a new member of the staff) develop or uncover precisely opposite qualities. This has its counterpart in the often-cited fact that even apparently intractable psychopaths suddenly settle down. In ordinary psychiatric practice, and indeed in ordinary life, qualities of egocentricity, opportunism, and affective coldness can be observed, without any history or particular likelihood of antisocial behaviour, in individuals who can only be classified as psychopathic if the bounds of the entity are stretched to a very wide and arbitrary extent.

Differences Between Chronic Offenders and Psychopaths

In practice nothing is gained by trying to draw a distinction between psychopathic and chronic offenders. The criteria often depend upon the tradition in the diagnostic service or on the available treatment methods. Psychopaths must be studied in prisons as well as in hospital; at any rate, lessons learnt from psychopaths will be applicable to certain chronic offenders.

It is also difficult to draw the line between aggressive and inadequate psychopaths: they seem to have many more resemblances than differences. Inadequate psychopathy can sometimes be observed to change into aggressive psychopathy, especially in adolescence. It has been shown (Gibbens *et al.*, 1959) that the subsequent offences of "aggressive psychopaths" are often not aggressive. Inadequate psychopaths sometimes break out into what have been called "catathymic crises" (Wertham, 1959), or autonomous affective crises (Gould, 1959), while in other inadequate psychopaths the motivation and pattern of offences closely resemble those of aggressive psychopaths. Thus, as Menninger (1938) has pointed out, some murders by aggressive psychopaths resemble some suicides by inadequate psychopaths.

Considerations for Research

Throughout the range of antisocial acts, whether set out legalistically or, more simply, as offences of a sexual nature, against property, against persons, or against the State, each may be the final common expression of widely differing individuals and motivation. As a corollary of this, whatever the abnormal or antisocial impulse may be—whether to kill, to steal, to practise some perversion—it will always be possible to find examples of those who do not act it out, of those who might if certain precipitating factors were to act strongly, and of those who do, or would, whenever the opportunity arises. This, together with the hard fact that, of all possible criteria for prediction, nothing seems so reliable as the simple record of offences, suggests that it may be advisable deliberately to study mechanisms of control rather than what is controlled. Possibly the comparison of offenders who have not repeated their offences for 10 years with recidivists would be valuable.

The very useful concept of Mayer-Gross *et al.* (1954) and of Schneider (1958) of psychopathy simply as a deviation from the statistical normal, which therefore includes the study of the whole range of abnormal and unusual personalities, is likely to be so wide as to be an unrewarding or impracticable approach from the point of view of research.

To study specific types of offenders—that is, selected according to their offence—would be useful, but limited for the reasons stated above.

Statistical factorial analysis would seem to be essential but as yet likely to be disappointing, for the reason that the method is dependent on the nature and accuracy of the material fed to it. One of the major obstacles in research will be the difficulty, in many cases the impossibility, of obtaining crucial information; for instance, on the early learning environment.

While the various analytical and deep psychological approaches have been disappointing from the treatment point of view, they have opened up areas of experience of which the importance had never been suspected—for example, the implications of the child–parent relationship. It may be that the immediate value of this approach will be in the choice of questions to be asked and in the technique of obtaining information. Such techniques could be operated most effectively with children whose parents would also be available, as in the Fels investigation into parental attitudes.

As compared with the more objective approaches (psychometric, physiological, anthropological, genetic) the investigation of hidden environmental factors has lagged far behind. Yet it would seem that enough evidence has now accumulated to demonstrate its importance and to warrant the concentration of effort in this direction.

Sources of Material

The available sources of material are the 25,000 individuals in prisons and Borstal institutions, the 8,000

young people in approved schools, the children in special schools under the Education Act ("maladjusted" and some of the educationally subnormal), patients in the mental deficiency and mental hospitals, the three State hospitals, possibly the reception centres (formerly casual wards) where the asocial drifters tend to accumulate.

It is suggested that the approved schools might prove a very valuable place for research operations for these reasons: (1) there is legal provision for detaining them, and for following them up over a statutory period of six years; (2) they are required to pass through (with rare exceptions) a classifying centre where the research team might operate both for initial assessment and for subsequent reassessment during the follow-up periods; (3) their parents will usually be available; (4) these schools are small enough to facilitate the study of every inmate, and sufficiently numerous and differently managed as to vary greatly in the sort of training and treatment provided; and (5) at this age the approved school is likely to be the first long-stay correctional institution which the inmates have experienced, so that there will be less likelihood of secondary "processing" by the penal machinery (a complication which may be very important in corrective training or preventive detention).

Classification of Psychopaths

Before studying the effects of treatment it seems essential to classify the material to be treated; experience shows that this cannot usefully be done by description of behaviour alone, because, as stated above, a piece of behaviour can be the final expression of very different motivations and personalities.

Excluding organic, epileptic, and psychotic illness, the following four subdivisions suggest a practical departure point for such a classification. Each is considered briefly under four headings: (*a*) the offender's attitude to his offence, (*b*) observations about the offence, (*c*) its impact on the observer, and (*d*) treatment required.

1. Trained, But to Antisocial Standards

Such offenders are behaving as they were taught to behave; they are doing what is "normal" in their families or districts. Some families, consciously or not, train their children to get what they want irrespective of the considerations of others; this is particularly likely to happen in large families, in which the siblings battle for supremacy and are checked from so doing by similar forceful means by their parents. This is what has been called subcultural crime, or "socialized delinquency" (Hewitt and Jenkins, 1946). A more subtle variant is where the parent is obtaining a vicarious satisfaction from the misbehaviour, as described by Johnson and Szurek (1952).

(*a*) The offender has learnt his behaviour consistently, he will not feel guilt about doing what he was taught to do. his family or circle will not be critical. This sort of crime is not inconsistent with a well-formed character in the individual.

(*b*) The offence is strictly goal-motivated, intended to gain something materially or as mastery or prestige.

(*c*) The observer may easily understand the behaviour and feel sympathy in the sense of finding it possible to identify with the offender and his setting.

(*d*) The treatment required is retraining; in its simplest form punishment is enough, especially if detection is certain and if the others of the subculture are treated at the same time. As with any punishment, it is likely to be most effective if not too severe or too lenient, and if there is some complementary "advice, assistance, and befriending" to make sure that the offender understands the wider implications of his behaviour and the rationale of society's reaction to it. Because the offender's personality is intact, his learning process is unfettered, and there will be no positive defence against learning another pattern of behaviour.

2. Reparative Behaviour

The offence here is part of an intelligently, laboriously, and often unconsciously worked out policy aimed at adjustment of the individual to difficulties in his environment or to the personal handicaps which that environment has produced in him. For example, some offenders are compensating through their crimes for a sense of inadequacy and inferiority; they tend to be assertive, arrogant, sensitive to slight, and are predisposed to defensive assaults, perhaps to breaking and entering, or to stealing powerful objects, especially cars and motorcycles. Some sexual offenders—for instance, the homosexual—may fall into this category; the child learns that, in some way, women are dangerous, and therefore substitutes some other sexual outlet. Rado (1949) has used the term reparative in his classification of sex offenders.

(*a*) Such an offender is identified with his pattern of misbehaviour, even proud of it, and may value it because it protects him from something more dangerous. He may feel guilt about himself, may neglect consequences, but is unlikely to feel guilt in relation to the offence. His personality is to some extent defective.

(*b*) The offence is distinctly goal-motivated, gaining something in the emotional field though there may be secondary material advantages which may come to take an important part. The offences are not rigidly stereotyped, though habit formation can make them so.

(*c*) The trained observer can readily understand and sympathize.

(*d*) Treatment again is retraining; but here there will always be a positive defensive system opposed to treatment, so that some form of psychotherapy will be required. It is often possible for the individual, spontaneously or with help, to change the reparative pattern to one which does not conflict with the law, so that resolution of the personality defect is not always necessary; this is why punishment sometimes works even in this category.

3. The Untrained Offender

Those in the above categories have learnt effectively; in this category they have not. Because there have been no steady standards of behaviour provided, or because there has been a lack of inducements (material or affectionate) to learn, the resulting adult is correspondingly without standards and weak in character. These are the individuals whose behaviour or conduct difficulties show themselves diffusely and from early childhood. They are likely to have been handled in an inconsistent manner with an unpredictable succession of punishment, connivance, or encouragement either from the one parent or as between several adult figures.

(*a*) The offender often genuinely wishes he could resist his impulses, tends to be confused by punitive measures, but lacks the ability to act with firmness and consistency.

(*b*) The offences are goal-motivated, often suggested by others, likely to be mixed in type, certainly not stereotyped, and not maladaptive—they could have "come off," and often do; when they do they are enjoyed.

(*c*) Again the pattern is understandable in terms of the weak personality and specific background of the offender.

(*d*) Treatment consists of long-term patient supervision with a background of sanctions. Here, especially, heavy punishment tends to lead to the fourth category, and thus

to defeat its objective. In mild cases ambulant supervision and supportive treatment may be sufficient (psychotherapy is not very effective), but in severe cases a sheltered environment with gradual reintroduction of responsibility is indicated.

4. Rigid Fixations

These are the individuals in whom frustration has been so overwhelming, probably at a critical point in their learning process, that learning has broken down and been replaced by a fixed, "maladaptive" pattern of response. The theory rests on ethological observations such as those of Maier (1949) on rats which, when forced to act in a no-solution situation, developed a stereotyped persistent pattern of response even though it resulted, every time, in punishment. Patrick (1934) observed human subjects in a comparable experimental situation, and found that they, too, gave up rational searching for a solution and fell back upon a stereotyped pattern of behaviour. Marquart's (1948) students showed similar maladaptive behaviour when faced with no-solution problems. These fixations persist in animals and humans after "vacations" outside the experimental situation.

Theoretical as these considerations may be, it is a matter of direct observation that there are certain offenders who, from an early age, show a stereotyped, non-adaptive, and non-goal-directed pattern of behaviour which persists unaltered despite long periods within a controlled environment, and is utterly unimproved by even severe punishment. Furthermore, the background always shows early experience of "frustration" consistent with the theory.

(*a*) This offender often helplessly dissociates himself from his behaviour, but may be genuinely remorseful and anxious about it. Despite attempts to rationalize it, he tends to feel bewildered about it, and the more intelligent covertly believe themselves to be insane.

(*b*) The offence is stereotyped, gains nothing but relief from immediate tension, and seems out of context with the situation—for example, in the degree of violence expressed.

(*c*) The observer cannot feel sympathy with the offender or the offence which is outside his experience. The behaviour appears to be compulsive but is not so, for it is not resisted.

(*d*) Little is known about the treatment, but experience confirms that punishment is useless. It is certainly possible to prevent the building up of the "no-solution" situation, and it is useful to find out to what extent the frustrating precipitating situation is specific or general. This is particularly important for those who are confined within institutions, for it may frequently be the case that, for example, in one-sex institutions the specific frustrating experience never arises, so that it is impossible, in that institution, to help the individual to overcome his particular difficulty.

Theoretical Consideration

To return to theoretical consideration, the rats could be cured of their fixation by "manual guidance," and, concerning humans, Marquart (1948) writes: "Guidance is of value for the elimination of an abnormal fixation but not a habit, and continued failure or punishment eliminates a habit but not a fixation." One supposes that the specific frustrating situation should be reproduced and the individual should be shown how to cope with it by the therapist at his elbow, in the situation with him. Perhaps this is what Stürùp (1952) does when holding a person indeterminately in Herstedvester, or Maxwell Jones *et al.* (1952) when holding a person within a critical group situation.

At all events we should take account of Marquart's (1948, p. 137) remark: "Resistance should be handled by attempts to determine its source rather than by pressure designed to break it." Ashley Weeks (1958) wrote: "The idea that one can control future behaviour in a desired direction by setting a person apart and doing something to change him is a fallacy exploded by the recidivist record." Control is the operative word here, and we are bound to agree with him; but with a different approach there is no theoretical reason why offenders of this type should not be altered in such a way as to modify their stereotyped behaviour.

The difficulty, of course, with any such elementary classification as this, is that a given offender almost invariably falls awkwardly into several of the categories. It may well be that the third category (the untrained) is almost invariably combined with the fourth (the fixed patterns). And, of course, the second category (reparative patterns), containing as it does the whole range of antisocial neuroses and antisocial character disorders, is grossly oversimplified. Yet such a scheme fits many clinical facts, and may prevent wasteful and fruitless attempts at assessing treatment methods on material of quite different types. Bearing in mind some such classification, it may now be useful to review the available therapeutic methods.

Available Therapeutic Methods

Our treatment methods are as yet so ineffective that the primary need, not to do further harm, still requires emphasis. Whenever possible, therefore, psychopaths should be kept out of custody, for detention carries risks of its own. As soon as offenders or the antisocially inclined are segregated there is the tendency for staff and inmates to consolidate at opposite poles; a hierarchy tends to develop among the offenders; a threat is thus offered to the staff which calls out a repressive authoritarian regime and the possibility of a vicious circle of resentment and counter-resentment.

The standard methods of combating this are summarized in the following headings brought up in discussion by a group of approved-school headmasters in Bristol: A full programme of constructive and recreational activities in which the staff participate; this often means a succession of not-too-long-term "projects," so that the individuals can experience some return for their efforts. Some hardship or real lack in an institution is a great boon, provided that it is within the community's capacity to correct; this of course was well known to all the pioneers but not, apparently, to the rich authorities who tend to supply their "problem" children on a lavish material scale. Divide the inmates into as many different sorts of groups as practicable; in some the staff should be active, but in others strictly in the background; every member of the community must be involved.

There should be opportunity to air complaints and grievances in free discussion groups (Fenton, 1957; *Lancet*, 1959) (one headmaster described what he called "natter-groups"* for his junior approved-school boys). Some self-determination should be entrusted to the inmates, depending on the maturity and morale of the group. Staff should be of both sexes and should be kept keen and tolerant through staff meetings, access to those with greater experience or a different approach from

*Natter "is a Scots word of long standing, probably derived from the Icelandic knetta, to grumble" (Brewer's *Dictionary of Phrase and Fable*, p. 640).

theirs, exchanges with other establishments, research projects, and refresher courses. Outside contacts of inmates and staff with the community should be encouraged and not made difficult by geographical isolation.

Such methods are very generally, if somewhat unevenly, found in approved schools, Borstal institutions, and prisons. They should be looked upon as essentials for community living, to which specific methods of treatment may be added.

Greater use of and experimentation with hostels would reduce the population and length of stay in closed institutions.

Confining our further considerations to treatment methods within hospitals, prisons, and other remedial institutions, we have first to consider the commonly held view as expressed, for example, by Dr. R. Bennett (1959) in the House of Commons, that the only treatment for the psychopath is custodial and the lapse of time, "ageing in custody," as he put it. This is unlikely to be true if only by virtue of the great variation within the category of psychopaths. For those individuals for whom it is true two necessities arise: to maintain as healthy and productive a regime as possible, and to make certain that the age at which release could take place is not overshot; this would best be done by grading of security within the institution, or range of institutions, with a flexible means of transfer from one grade to the other, and by having an effective aftercare system. Much devoted work in institutions is thrown away through lack of aftercare.

The remaining principles of treatment are the familiar methods of individual psychotherapy, often difficult to apply to psychopaths, especially in prison, but maintaining a useful place. In a valuable paper, Mackwood (1949) describes the careful piecing together of the patient's history—the therapist, as it were, holding a mirror before him and enabling him to see his misbehaviour as part of his life pattern, a method which one would suppose to be useful, especially in the milder forms of our third category.

The difficulty is often in getting patients, especially those in the second (reparative) category, to the point at which they will co-operate. To this end the indeterminate sentence has been held to be of value or the indispensable corner-stone of treatment as in Scandinavia (Stürup, 1952; Aungle, 1959) and in some of the States of the U.S.A. (Boslow *et al.*, 1959). Undoubtedly the indeterminate sentence is valuable, but it would seem to be of doubtful value for the fourth (fixed) category—the one most likely to call it into operation.

Stürup (1959) describes his dynamic growth therapy and the utilization of "affective moments" (spontaneous catharsis) in changing a patient's point of view, while Maxwell Jones *et al.* (1952) use group pressures to bring a new awareness of his behaviour to the patient: both methods may be applicable to the second, possibly also to the third and fourth, of our categories.

Non-directive therapy (Rogers, 1942; Snyder *et al.*, 1947), group-guided interaction (Weeks, 1958), psychodrama (Moreno, 1946), and closed-group analytical psychotherapy in prison (Landers *et al.*, 1954) are now familiar terms indicating a considerable accumulation of experience, but largely unassesesd in their efficacy.

Therapy based directly on Pavlovian theory—for example, Wolpe's (1958) therapy by reciprocal inhibition, or Raymond's (1956) aversion therapy for sexual perversion—may have a useful place, but is unlikely to be effective with the fourth category.

Pharmacological (oestrogens, disulfiram, sedatives) and surgical (castration, leucotomy) treatment of physically normal individuals is favoured in some quarters, and may be regarded as another form of physical rather than psychological restriction or control, and is thus open to all the shortcomings of such methods. Such measures should not be confused with the pharmacological or surgical treatment of specific psychiatric conditions—for example, epilepsy or brain damage—which is an entirely different matter.

This may be the point at which to acknowledge that, with psychopaths, highly refined psychotherapeutic procedures, applied by medical men, are often no more successful, sometimes less successful, than the simpler and less esoteric approaches of certain social workers, probation officers, institutional staff, who may have had little or no training apart from on-the-job experience. Many psychiatrists with experience of working in remedial establishments would agree that a sympathetic member of the staff capable of winning the individual's respect and able to be with him when day-to-day crises appear is able to effect more than a psychotherapist who sees that individual at stated times. It is an established fact that patients who leave hospital with a bad prognosis after failing to improve as regards their psychopathy may then do well under probationary supervision. Such matters need further investigation; it may be that those in category four (the fixed patterns) are more responsive to this direct guidance from someone at their elbow and sharing the experience than they would be to many psychotherapeutic procedures. Some workers intuitively obtain good results with certain psychopaths; it should be possible to find out how they do it.

Conclusion

All forms of treatment of psychopaths are as yet inadequately, or not at all, assessed, and, furthermore, it would seem that a variety of methods are being applied without adequate assessment of the individuals to be treated.

Some such classification as put forward here and applied uniformly in observation and classifying centres (Scott, 1959) would seem essential for further progress.

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HORMONES AND CELLS

[FROM A SPECIAL CORRESPONDENT]

The Society for Endocrinology's symposium on "Cell Mechanisms in Hormone Production and Action" was held in London on May 3 and 4. By its terms of reference the symposium was to be an ordered inquiry into the synthesis and transport of hormones and the mechanisms whereby their influence is exerted in the cells of the target organ; its premise was that the hormone could be regarded as the bearer of partially interpreted genetic information.

Genetic Control

The importance of genetic control of hormone production was borne out by the content of the first two papers. W. R. TROTTER pointed out that the defects of single-gene mutations were well seen in certain forms of thyroid defect in man, notably in Pandred's syndrome, which could be shown to be inherited with a typical Mendelian 3:1 ratio. The condition is attributed to an inability of the thyroid gland to concentrate and take up iodine from the circulating blood, a fault that in turn is possibly due to a deficiency in the production of the enzyme peroxidase. Four other steps in thyroid-hormone synthesis have become recognized as gene-determined, and for one of these—the step involving the removal of iodine from thyroxine—the relevant enzyme "deiodinase" has actually been isolated.

A. C. ALLISON emphasized the central position of the protein enzymes and protein hormones in mediating gene effect. He maintained that genic influence found expression basically in two ways: in controlling amino-acid substitution in protein chains, and in making possible the occurrence of polymerization or aggregation of protein molecules. The small yet highly significant variations in the arrangement of amino-acids in some pituitary hormones could well have been evolved through the ages as the result of mutation of specific genes. Genic control would be exerted during the synthesis of the enzyme or the protein hormone, and the cell structures most probably involved in these syntheses were identified as the minute R.N.A.-containing granules lining the cytomembranes, granules now referred to as ribosomes.

Studies in the fine structure of the cell revealing the varied distribution and abundance of ribosomes in different cells were described by SYLVIA FITTON JACKSON, while P. N. CAMPBELL provided impressive biochemical evidence of the part played by rat-liver ribosomes in the synthesis of serum albumin. But ribosomes, it seems, do not function alone, and some part in synthesis is played by the cytomembranes, and probably other structures too, notably the mitochondria. Indeed, as ROSALIND V. PITT-RIVERS pointed out, though thyroxine synthesis *in vitro* can occur in tissue slices and even in isolated cells, homogenates produced only monoiodotyrosine, which suggests that in some way the organization of the living cell as a whole is essential to the process. SYLVIA FITTON JACKSON suggested that secretion of substances of higher molecular weight than could reasonably be held to pass through the plasma membranes might take place through the production of relatively simple components which aggregated on reaching the outer surface of the cell. Variations of cell surface with function were mentioned by J. K. GRANT, who described how stress-invoked changes in adrenal cortical cells included the formation of microvilli, probably associated with increased hormone secretion.

The forms taken by some hormones during transport in the blood-stream were discussed by some speakers. I. H. MILLS reported that cortisol, and probably also other steroid hormones, are largely bound to plasma proteins during transport, and the same, according to J. R. TATA, was true of the thyroid hormones. In both instances the α-globulin fraction of the plasma was implicated.

Do Hormones Enter Cells?

When the hormone reaches the target cells it must somehow exert its effect on or through the cell surface. The need for a clearer understanding of the nature of the cell surface was stressed by L. WEISS, who argued that heterogeneity in cell-surface structure was probably much greater than commonly realized and that actual entry of the hormone into the cell need not necessarily occur; information could conceivably be imparted through a molecular reorientation process, possibly at specific sites on the surface.

Whether or not the hormones enter cells, various factors may modify their influence. F. G. YOUNG noted that the degree of oxygenation of the blood apparently affected the activity of the circulating insulin, a relationship that might hold with other hormones also. Metabolism of thyroid hormones yielded simpler compounds which still had the capacity to stimulate metabolism, but J. R. TATA believed that the true hormonal influence is carried only by thyroxine and triiodothyronine.

Hormones and Cell Metabolism

Several reports were concerned with the mode of action of hormones on cell metabolism. The action of insulin was considered by G. HOWARD SMITH to be essentially that of increasing the permeability of cells to glucose; he postulated a sugar-carrying mechanism in the cell which was controlled through inhibition by adenosine triphosphate, the action of insulin being to inhibit A.T.P. inhibition. A. KORNER, K. L. MANCHESTER, and E. REID described excellent independent investigations bearing upon the action of various hormones on amino-acid incorporation, protein synthesis, and components of protein-synthesizing systems. Effective agents were growth hormone, A.C.T.H., insulin, L-thyroxine, and certain corticosteroids.

These studies have the special significance that they are concerned with ways in which hormones might influence the production of hormones, and thus may ultimately provide a biochemical explanation for the integration of the endocrine system.

The mode of action of oestrogens remains as deep a mystery as ever, but the painstaking studies with oestrogen antagonists, described by C. W. EMMENS, hold promise of yielding valuable clues in the near future.

JOINT MEETING OF BRITISH AND DUTCH ORTHOPAEDIC SURGEONS

[FROM A SPECIAL CORRESPONDENT]

The spring meeting of the British Orthopaedic Association was held in Glasgow from April 7 to 9 in conjunction with the Dutch Orthopaedic Society and the Hand Clubs of Great Britain. The president, Mr. H. J. SEDDON, was in the chair.

Dye Determination of Tissue Viability

Among the many subjects discussed were several of particular interest. In the symposium devoted to hand surgery Mr. M. N. TEMPEST (Chepstow) presented an ingenious method of determining the viability of tissue in a fresh injury or burn. He had injected intravenously a dye, either disulphine blue or Kiton fast green. This stained all living tissue, but avascular tissue remained unchanged. 230 observations had been made: 3–5 minutes after injection maximum staining was obtained. The dye was excreted by the kidney in about 48 hours.

Two speakers presented papers on an always controversial topic: the stiff and painful back in children. The authors had deliberately excluded Pott's disease from their considerations. Mr. N. J. BLOCKEY (Glasgow), in conjunction with Mr. J. SCHORSTEIN (Glasgow), reported 12 cases of children with stiff, painful backs. The symptoms were caused by: spondylolisthesis, 3; prolapsed intervertebral disk, 1; osteoid osteoma, 1; extradural abscess, 2; tuberculous spinous process, 1; implantation epidermoid, 4. They described the first and the last of these conditions. Spondylolisthesis had presented as a very painful stiff back in a child. The white-cell count and sedimentation rate were raised but the temperature was normal. There was no response to penicillin. At exploration a disk was found to be bulging and tense. On being incised there was no pus, but a *Staphylococcus pyogenes* sensitive to chloramphenicol was isolated, and on this drug the condition rapidly cleared up.

A Hazard of Lumbar Puncture

Four children with rigid backs were found on myelogram to have filling defects in the lumbar region. On exploration these were found to be epidermoid implants lying intrathecally. All four children had previously had lumbar punctures which had been done with an intravenous needle. This type of needle was particularly likely to carry in with it a plug of skin and should be avoided.

Mr. A. MCDOUGALL (Glasgow), in conjunction with Mr. J. M. ROBERTSON (Glasgow), described the occurrence of prolapsed intervertebral disks in adolescents, which, they said, was not as uncommon as was generally supposed. In this age-group the onset was insidious, with pain in the back and buttock. Neurological changes were less common than in the adult because the nerve root could adapt itself more easily and avoid compression. The results of conservative treatment were unsatisfactory, but after operation recovery was rapid.

Congenitally Dislocated Hips

Any observation likely to help with the prognosis of a congenitally dislocated hip before treatment is started is welcome, and Mr. J. WILKINSON and Dr. C. CARTER, of the Hospital for Sick Children, Great Ormond Street, had, with this in view, investigated the results of treatment in 200 children suffering from this condition. With a follow-up period of 5–10 years they had come to the conclusion that conservative treatment in bilateral dislocations was rarely successful, but could be successful when the condition was unilateral. In the course of this investigation they had observed that when dealing with unilateral dislocations the condition of the "other" hip had a considerable bearing on the prognosis. If, after allowing for age and sex, the opposite acetabular roof appeared to be unduly sloping the prognosis was the same as for bilateral dislocations—that is, poor—whereas if the opposite acetabulum was normal the prognosis was good. They concluded that bilateral dislocations and those unilateral dislocations in which the prognosis was bad should be treated operatively.

At the other end of the scale are those hips with residual subluxation which in later life have become arthritic. This problem was discussed by Dr. G. F. J. M. BÄR (Nijmegen). He advocated the shelf operation in such cases. The shelf was made by turning down a flap of ilium over the femoral head. The effect of the shelf was due to the support it gave to the femoral head. This prevented further displacement, reduced irritation of the capsule, and corrected muscle imbalance. The mechanical correction improved the texture of the bone. Of 114 hips followed up, 96 showed great improvement, and 18 were failures. Failure was due to the shelf being too small, too high, or not well placed.

Bony deformity frequently develops in children with poliomyelitis. This can readily be corrected by osteotomy, but rapidly recurs. The nature of this remodelling of the bone was discussed by Mr. M. S. BRETT (Salisbury) in a review of osteotomies correcting deformity around the knee. Theoretically correction could occur by remodelling at the osteotomy site or at the epiphysial line. He was able to demonstrate that the greater part of the correction took place as the result of differential growth at the epiphysis. The most rapid correction was 35° in 20 months.

Bone-grafts

The supply of bone for a bone-graft can present a major problem. There is little doubt that an autogenous graft is better than bone from any other source, but it is not always readily available. Dr. M. J. KINGMA (Amsterdam) discussed the relative merits of heterogenous and homogenous bone as graft material. Great experience with heterogenous bone has been gained by Dutch orthopaedic surgeons, who were able to obtain refrigerated calf-bone from the Bone Transplantation Service of the Netherlands Red Cross. He was able to say, after much use, that this bone had only a very limited application. The patient must be young, the contact of the graft good; and there must be firm fixation and prolonged immobilization. He thought the only use for this type of bone was for filling bone cavities in children. Homogenous grafts refrigerated at −55° C. were much more efficient, but took longer to incorporate than autogenous bone and should be used only if autogenous bone was not available.

Dr. O. VERBEEK (Amsterdam) discussed the use of bone-grafts in the treatment of ununited fractures of long bones. He said that while bone-grafts took a long time to revascularize after implantation they retained their strength for five months. For this reason they acted as a good form of internal fixation—but needed prolonged protection from strain. Autogenous grafts, on the other hand, were rapidly revascularized and incorporated but soon lost their strength, so that they were less effective for internal fixation. But the autogenous graft was more osteogenic than the homogenous one, and promoted bony union more quickly. They could be used together to bridge gaps, the autogenous graft to provide osteogenesis and the homogenous graft to provide internal fixation.

Mr. J. CHALMERS (Edinburgh) said there was a widespread belief that immature tissue used as a homograft would become incorporated more quickly than mature tissue. He had carried out experiments on mice in which foetal femora were implanted into adult mice as isografts (grafts from the same pure strain) and homografts. The animals were killed at intervals of from two days to three months. Bone-grafts grew normally for six days. After that the isograft had become incorporated; the cartilage grew and was replaced by bone in the usual way. But in the homografts bone replacement ceased and the bone died. The cartilaginous

part of the graft continued to grow. This was strictly in accordance with homotransplants of adult bone and cartilage, and suggested that nothing was to be gained by transplantation of immature tissue. It was interesting to note that, as the isograft continued to grow with progressive replacement of bone but not subjected to the normal stresses, the secondary characteristics of the bone disappeared. In the homograft, where the cartilage continued to grow but was not replaced by bone, the shape of the bone accurately persisted, all the secondary characteristics being well defined.

New Appliances

MODIFICATIONS OF THE GERSHOM THOMPSON PUNCH

Mr. J. E. SEMPLE, senior surgeon, St. Paul's Hospital, London, writes: The Gershom Thompson punch is a beautifully designed instrument which fulfils completely the needs of the majority of urologists. But many surgeons find that some small modification in an instrument may suit a personal technique or remove a cause of delay or irritation and so allow an operation to be carried out more easily. A record of delays and breakdowns in four separate Gershom Thompson punches has been kept over a number of years, and modifications in order to reduce these delays have been tried out and adopted (Fig. 1).

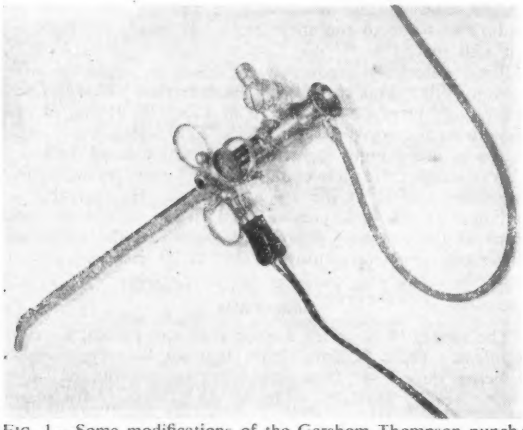

FIG. 1.—Some modifications of the Gershom Thompson punch: (1) the recessed blade, (2) a two-pronged plug replacing the Wappler switch-post, (3) two finger-loops and a Swinney thumb-loop to enable the punch to be used with one hand, (4) pilot light, not shown, as it was placed between the lead and the battery, and (5) bubble-release mechanism replaced by a direct outlet.

1. In certain types of prostatic obstruction the gland tissue does not readily bulge into the cutting chamber, and the punch has to be depressed with considerable firmness on to the gland, with resulting trauma to the point of fulcrum—the membranous urethra. The standard blade cuts parallel to the sheath of the punch, the plane of the cut being dependent on the direction of the blade and the pressure and counterpressure between the gland tissue against the outer surface of the blade just below the cutting edge (Fig. 2). By grinding a groove immediately below the cutting edge and increasing the angle of the bevel of the blade, the cut can be made to run more outwards and deeply into the gland, thereby increasing the size of the piece of tissue resected (Fig. 3). When this type of blade was compared with the standard blade the fragments removed were found to be twice those of the standard blade. It was also found that the deeper the groove the more deeply the blade cut, so that in fact this blade became self-feeding.

2. The standard type of electrical connexion between the lead and the punch is a Wappler type of switch-post. The record of the four punches showed frequent breakdowns in this electrical connexion. Such breakdowns were almost eliminated by substituting a two-pronged plug and modifying the switch-post to take it (Fig. 1). But even the standard Wappler connexion can be made very much more reliable by having two knurled thumb-screws tapped through the outer and inner coats of the lead connexion, so ensuring

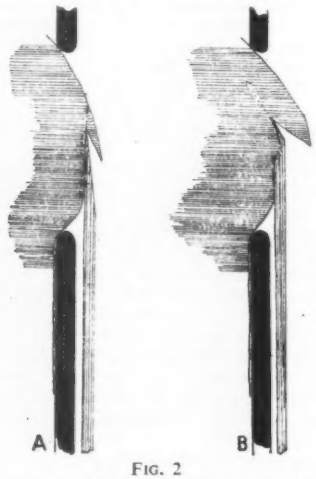

FIG. 2

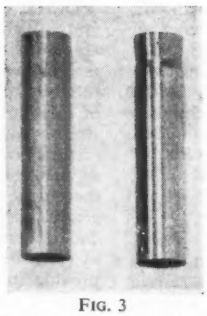

FIG. 3

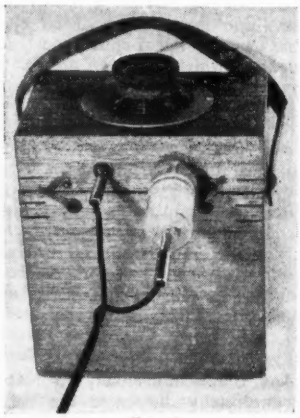

FIG. 4

FIG. 2.—This shows the prostate gland bulging into the cutting chamber (the sheath of the punch is shown by thick black lines) and how the plane of the cut depends on the direction of the blade and the pressure and counterpressure of the cut gland tissue on the blade just below the cutting edge (A). A recess ground just below the cutting edge allows the plane of the cut to be directed far more deeply into the gland (B).

FIG. 3.—A recessed blade (on the right) compared with the standard blade.

FIG. 4.—Pilot light. This consists of a spindle of "perspex" holding a six-volt standard torch-bulb. At one end of this spindle is a thin metal rod which plugs into the terminal of the battery or transformer; the current is conducted along this rod and through the bulb, which is connected to a metal tube at the opposite end into which the terminal of the lead is inserted. The bulb will glow only when the lamp of the punch is alight. As a result of using this pilot light, the withdrawal of the punch from the bladder and the trauma of reinsertion have been frequently avoided when vision has been so obscured as to raise doubts whether the lamp of the punch had burnt out. Pilot lights situated between the punch and the lead were tried, but were discarded as they upset the balance of the instrument.

better electrical contact between the lead and the switch-post as well as rendering it more rigid.

3. Two finger-loops—one on the upper surface of the barrel of the punch, which protects the electrical connexion, and one on the under surface. A Swinney thumb-loop controlling the flow of irrigating fluid allows the punch to be used with one hand (Fig. 1).

4. A pilot light is inserted at the battery end of the lead, to obviate the necessity of removing the punch to see if the bulb of the punch has burnt out (Fig. 4).

5. The air-bubble-release mechanism on the eyepiece was shown to become frequently blocked by debris and blood-clot. If one of the two standard eyepieces supplied with the punch has the air-bubble-release mechanism replaced by a simple direct outlet through the upper part of the side of the eyepiece, to which a piece of rubber tubing of suitable calibre can be fixed, delays through obscured visibility will be much reduced (Fig. 1).

I would like to acknowledge the skill and co-operation of the Endoscopic Instrument Company in carrying out these modifications.

Nova et Vetera

JAMES DOUGLAS OF THE POUCH, 1675–1742*

The name of James Douglas is commonly in use by the anatomist and the gynaecologist, yet little is known about a man who spent a lifetime in the service of these subjects, who was a fine botanist and zoologist, whose collection of the works of Horace was unparalleled, and who, besides, taught and inspired the great William Hunter, filling him with an admiration which lasted to the end of his life. When Hunter died in 1783 he bequeathed all his treasured collections to Glasgow University, where they formed the basis of the splendid Hunterian Library and Museum. Among the documents are some 63 manuscript pamphlets,[1] on subjects ranging from lithotomy to lexicons, from knee-joints to chocolate, all written by James Douglas, and almost all unpublished. In addition, there are 29 large bundles of manuscripts, uncatalogued and unpublished, the majority from Douglas's own pen, forming an important and interesting source of information on medical practice in the 1700's, and containing case-notes, clinical descriptions and prescriptions, anatomical studies, investigations into natural history, and such curiosities as the verbatim confession of Mary Tofts, the "rabbit-producing" woman of Godalming, with whose exposure Douglas was closely concerned in 1726.

These documents are in course of more detailed study, and a catalogue is in preparation.

In addition to many papers read to the Royal Society, to which he was elected in 1706, Douglas published three anatomical books, two on botanical subjects,[2,3] and a catalogue of his Horatian library.

Douglas was very early in the field of private lecturers of anatomy in London, for in 1707 he was advertising *An Account of what Dr. Douglas obliges himself to perform in a Course of Human and Comparative Anatomy:* this comprehensive course was given three or four times yearly, at a charge of three and a half guineas. In this year also, he published his anatomical textbook, *Myographiae Comparatae Specimen, or a Comparative Description of all the Muscles in a Man and in a Quadruped* (12mo). This is an attractive, well-ordered, and accurate little book; the quadruped of the title is the dog, which has an honourable history in anatomical investigation, and which he chose, Douglas says, because of its ready availability to young students. In this book Douglas lays claim to no fewer than thirteen muscles as his own in priority of description, but it is curious that none of these has achieved eponymic recognition, which has been reserved for structures described only meagrely by him, if at all. Of these, two, the "semilunar fold"† and the "line of Douglas,"‡ have not been found anywhere described. The other eponymic features are the "pouch of Douglas" and its associated "ligaments of Douglas," the peritoneal folds which limit it laterally. This was mentioned in Douglas's best-known book, the *Description of the Peritonaeum*, 1730 (4to). The manuscript is in the Hunterian Library (Young's cat. No. 543); on the flyleaf are the words "already printed," in the handwriting of William Hunter. On page 37 of the printed version appears the passage from which the eponym is derived: "Where the peritonaeum leaves the foreside of the rectum, it makes an angle, and changes its course upwards and forwards over the Bladder: and a little above this angle, there is a remarkable transverse stricture or semioval fold of the Peritonaeum, which I have constantly observed for many years past, especially in women." It cannot be claimed that this is a highly detailed, or even accurate, description, and the origin of the phrase "pouch of Douglas" is very obscure, as it does not begin to appear in the textbooks for over a century.

Douglas's unpublished works at Glasgow cover a huge field, and his gift for true observation and clear expression is well exemplified by his descriptions of pathological anatomy, a few only of which were published in the *Philosophical Transactions*, of the many which he showed to the Royal Society.

A notable case was seen at St. Bartholomew's Hospital, where he performed a necropsy on a young man with aortic and mitral stenosis and incompetence. Douglas had both felt the "thrill" and heard the murmur by the bedside (*Phil. Trans.*, 1716, No. 345). Yet this was 1716, a century before Laennec.

Douglas wrote his case-notes at the bedside, some as early as 1704. Many diseases are noted, such as chlorosis, abortion, inflammation of the tonsil, cancer and prolapse of the uterus, and many cases of smallpox. Physical examination was performed in many instances, "touching"—that is, per vaginam—being apparently a routine in appropriate cases.

His treatment was of the contemporary orthodox style, Galenic and humoral, consisting mainly of purging and vomiting, venesection being rarely performed. Drugs were very freely prescribed, but his only useful ones were opium, mercury, and drastic purgatives. A commonly used phrase was "these wrought both up and down."

Of his personal life little is known. Douglas was born at Baads, near Edinburgh, in March, 1675, the second son of a landowning family.§ A younger brother was John (died 1743), who reintroduced the operation for suprapubic lithotomy in 1719.

James graduated M.D. Rheims, and came to London in about 1700. He married Martha Wilkes, aunt to the reformer John Wilkes, and they lived in Covent Garden and Red Lion Square. Their daughter, Martha Jane, became engaged to William Hunter, but she died in 1744, aged 28. Their son, William George, was in part responsible for the introduction of William Hunter into the household; for Hunter, arriving in London in 1741, at first stayed with William Smellie, and in August became Douglas's assistant and tutor to his son. The death of Douglas in April, 1742, placed Hunter in a difficult position, but he determined to remain in London, and stayed on in the house of Mrs. Douglas till 1749, being joined there by his younger brother, John, in 1748.

William Hunter gives a poignant picture of the death of James Douglas, writing to his mother: "Early on the

*Condensed from a paper read to the Section of the History of Medicine at the Joint Annual Meeting of the British Medical Association and Canadian Medical Association, Edinburgh, 1959.

†The curved lower free border of the posterior sheath of the rectus abdominis muscle.

‡The lower edge of the internal oblique muscle, merging into the conjoined tendon.

§The present representative of the family is Viscount Chilston, who still owns part of the estate of Baads.

morning of Dr. Douglas's death, I was called at his desire: he snatched at my hand and spoke a few words: he would not let me go out of the room: I sat on his bed till after noon when he expired with his hand locked in mine. . . ."

This modest letter indicates the impression made by this pupil on his teacher after seven months' acquaintance. Can it be doubted that the impression made by the teacher on the pupil was any less?

James Douglas's most important claim on posterity is his influence on William Hunter and on his subsequent work and investigations.

Hunter has, in part, repaid his debt to Douglas by the careful preservation of his writings, now in Glasgow.

I am grateful to Mr. R. O. McKenna, Librarian of the Hunterian Library, for much help, and to the Trustees of the Wellcome Trust for a grant to cover expenses.

K. BRYN THOMAS.

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3 Douglas, James, *Arbor Yemensis fructum Cofé ferens: or, A Description of the Coffee Tree*. London. 1727. Folio.

THE STEPS OF NATURE

Professor Singer took his degree in the Final Honours School of Zoology at Oxford before proceeding to the study of medicine, and from time to time he has returned "with a recollected love" to illuminate the history of biology. This is the third edition of his well-known book on the subject which first appeared in 1931.* It has been revised throughout and altered without impairing the simple language of the original presentation. It ends like its predecessors with the nineteenth century, but mentions a number of existing unsolved and possibly insoluble biological problems.

The book is encyclopaedic in its range and masterly in its study of evolution. Although in speaking of William Harvey attention is chiefly devoted to his discovery of the circulation of the blood, Professor Singer does not forget his contribution to embryological thought. On p. 474 he mentions Harvey writing that Nature, "by steps similar in all animals, goes through the forms of egg, worm, embryo, gradually acquiring perfection at each step" (1628). Finally, the author observes, "Competing with and interwoven with the problems of heredity and reproduction are the problems of the chemistry of living matter and the origin of life itself." These questions are the chief study of many biologists to-day.

ARTHUR S. MACNALTY.

**A History of Biology to about the Year 1900: A General Introduction to the Study of Living Things.* By Charles Singer. Third (revised) edition. (Pp. 580+xxxvi; illustrated. 50s.) London and New York: Abelard-Schuman. 1959.

(*Continued from next column*)

The proportion of patients who become "secondary failures" varies from about 5% to 20% each year according to the type of patient treated and the standard of diabetic control accepted as being satisfactory.

Side-effects.—The remarkable freedom of tolbutamide from toxic effects renders it almost unique among drugs of therapeutic importance. Allergic skin reactions, usually mild, occur in about 5% of patients; a similar number experience some dyspepsia and occasionally diarrhoea. A few patients treated with tolbutamide become very susceptible to the intoxicating effects of alcohol. Hypoglycaemic reactions seldom occur unless insulin is also being administered. Hepatic and renal functions are unaffected, and very few serious blood dyscrasias have been reported.

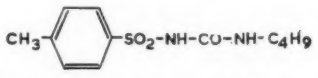
N.H.S. Basic Price.—100 0.5-g. tabs., 22s.

To-day's Drugs

Tolbutamide

"Rastinon" (Hoechst).

Chemistry.—This is N-(*p*-toluenesulphonyl)=N'-(n-butyl)-urea:



Pharmacology.—Tolbutamide is one of several sulphonylureas which, when given orally, reduce the concentration of glucose in the blood of experimental animals and human subjects capable of secreting some endogenous insulin. The immediate fall in glycaemia is almost entirely due to reduced release of glucose from the liver. Two main hypotheses have been devised to account for the drug's action; they differ essentially in the role they assign to insulin. The first holds that the hypoglycaemic effect is due to the action, on the liver and peripheral tissues, of the additional insulin liberated after taking tolbutamide. This hypothesis assumes that insulin directly inhibits hepatic release of glucose; but there is little evidence for this, and much against it. The second attributes the fall in glycaemia to the direct action of the sulphonylurea on hepatic metabolism in the "permissive" presence of enough endogenous insulin. The explanation of how the sulphonylureas act is thus unknown, but it should probably embrace elements of both the above hypotheses.

Therapy.—Tolbutamide has no hypoglycaemic effect in diabetes of the juvenile insulin-dependent type, but reduces the glucose concentration in the blood of most mild insulin-independent diabetics. However, fully half of the latter can and should be controlled by dietetic restriction alone. In general, therefore, only those who developed diabetes when aged more than 35 years, whose symptoms were and are relatively mild and slow in progression, and who are neither overweight nor much underweight are suitable for attempted treatment with tolbutamide. Such newly diagnosed diabetics should be given a trial period of dietetic treatment, and only if this fails is tolbutamide given; about three-quarters of them will then respond satisfactorily to it. The same clinical criteria apply to the selection for trial of tolbutamide treatment of patients already being treated for established diabetes. The attempt to substitute tolbutamide for insulin must be conducted with considerable care, and those patients taking more than 40 units daily should usually be admitted to hospital. When the insulin is discontinued, the patient must test urine specimens daily for glucose and acetone during the next fortnight. A few, in spite of having been previously well controlled with as little as 24 units of insulin, will quickly show ketonuria and considerable glycosuria, and must immediately revert to insulin treatment; about a tenth to a fifth of them will remain aglycosuric on diet alone; the remainder sooner or later show glycosuria, and about two-thirds of them will respond satisfactorily when treated with tolbutamide.

Tolbutamide is taken twice daily, with breakfast and the evening meal, or occasionally thrice daily. The dose required varies from 1 to 3 g. each day, and no one dose should exceed 1.5 g. Tolbutamide treatment does not alter the post-prandial rises or daily pattern of glycaemia, so that the blood glucose increases during the day and may rise from low fasting levels to very high values in the evening; for this reason tests not only of overnight specimens of urine but also of those passed in the evening—after supper or before going to bed—are required to assess control of the disease properly. Diabetics treated with tolbutamide must test these urine specimens on one day every week, since some of them become resistant to its hypoglycaemic action and the disease becomes uncontrolled.

(*Continued at foot of previous column*)

Correspondence

Doctors in South Africa

SIR,—May we plead the hospitality of your columns for an appeal to all those who share our concern about what is now going on in South Africa? The racial policy of the South African Government has for many years involved serious questions of principle for the profession. These have included the enforcement of unscientific theories in the conduct of the blood transfusion services; the Act introducing apartheid into the nursing profession (with a £200 fine for anyone who "permits any White person . . . to be employed under the control or supervision of any . . . person who is not a White person, in any hospital or similar institution."—Nursing Amendment Act, 1957, IV, Section 49); and the impossibility of holding any international scientific meeting within the Union, without humiliating many of the delegates.

Recent events have shown the consequences of this policy. But the ways in which it has involved our South African colleagues are as yet too little known. We now have news of warrants for the arrest of 12 of our colleagues, without charge, under the emergency regulations (Dr. Max Joffe, April 23, p. 1279), and no doubt there are others of whom we have not heard. These laws make it a criminal offence even to publish the names of those arrested, and it is ironical that many South African doctors will only know of the arrests through the columns of the British medical press.

We believe that the profession in this country has a responsibility to our colleagues in the Commonwealth who have now been deprived of the elementary right to pursue their work unhindered by racial dogma. We believe the weight of opinion on this matter is so great that a continuing body of some kind could usefully be formed, with the objects of: (1) Acting in whatever ways we can to support those South African doctors who are facing persecution for their adherence to civilized beliefs. (2) Obtaining information as to the plight of our colleagues, and as to the legal impediments to the pursuit of their calling without racial distinction, regarding either doctor or patient. (3) The publication of such information to the profession both here and in South Africa. (4) To ascertain what medical facilities are in fact available to the general population in South Africa. We ask all who support us in this, or have other suggestions, to contact Dr. Eleanor Ettlinger, 20, Lansdowne Crescent, London, W.11, who has kindly agreed to do the work involved in convening a meeting in the near future.—We are, etc.,

AMULREE,
ALECK BOURNE,
P. D'ARCY HART,
R. D. LAWRENCE,
R. MAC KEITH,
N. MALLESON,
D. MORRIS,
NORMAN MORRIS,
W. C. NIXON,
D. O'NEILL,
H. OSMOND-CLARKE,
DAVID PITT,
SIMON YUDKIN.

Chemical Carcinogenesis

SIR,—The practical implications of chemical carcinogenesis as a hazard to man are being taken seriously by many people. The "cranberry incident" in the U.S.A., other less publicized effects of the new U.S. regulations governing the occurrence of carcinogenicity in food additives, and your recent leading article on "imferon" (March 12, p. 788) all emphasize the serious consequences that may result from an acceptance of the principle that cancer may, at least in part, be a problem in preventive medicine.

In this new and in our view long overdue role information obtained in the cancer research laboratory must be evaluated with considerable care. The labelling of any substance as a carcinogen is now a serious matter that may easily cause a major disruption of our lives. In an annotation (March 19, p. 868) you stated that 16 carcinogens of various potencies have now been reported in tobacco smoke; some of the compounds mentioned are certainly carcinogens; others indiscriminately included in the list are dubious indeed in this respect. Chrysene, for example, has been investigated on many occasions; most reported studies are negative and those reporting the induction of an occasional tumour in animals are suspect of contamination with other compounds. 3-Methylpyrene (or some other alkyl derivative) is, to say the least, an inadequate description. The 11:12-benzfluoranthene classified with the other two related compounds was negative in one reported study and gave rise (in our view) to an insignificant number of tumours in the other. 1:12-benzperylene must have been tested very recently, since we are unable to find any data on this material.

Arsenic is suspect as a carcinogen in man in inorganic form; in animal tests many derivatives of arsenic have yielded negative results. From your annotation all forms of arsenic might be condemned. One could continue with other examples; let it suffice to say that the greatest caution should be observed in classifying a material as a carcinogen. No blanket statements of this sort should find a place in the authoritative editorial columns of a responsible professional journal. If to-morrow a food additive is found to be contaminated with 3-methyl (or some other alkyl) pyrene, it would be in danger of being banned on the authority of your editorial columns.—We are, etc.,

PHILIPPE SHUBIK.
WILLIAM LIJINSKY.

Division of Oncology,
The Chicago Medical School,
U.S.A.

*** Our annotator writes: E. L. Wynder[1] listed chrysene as a carcinogen, with references; Wynder and Hofman[2] have reported 3-methylpyrene and 11:12 benzfluoranthene to be carcinogenic: Sir Ernest Kennaway first showed 1:12 benzylperylene to be so, as has been confirmed by Wynder and other independent workers.[3] The interpretation to be placed on findings of this kind has been fully discussed by Kennaway,[4] who was of the opinion that no minor carcinogen should be regarded as negligible. With regard to arsenic, the term as used in connexion with partial combustion products always has been understood to mean arsenious oxide (As_2O_3), as this is the form in which the element is found in such products. The oxide is without doubt carcinogenic.—ED., *B.M.J.*

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"Imferon" and Cancer

SIR,—Your correspondent Dr. Cyril Helm (May 7, p. 1429) asks a pertinent question as to whether a case of cancer has been known to occur after injection of "imferon" in a human being. In the same issue there was the report on metastatic carcinoma at the site of injection of iron dextran complex by Dr. J. D. Crowley

and Dr. W. J. S. Still (p. 1411). In this case it is suggested that the iron dextran determined the site of the metastasis and did not initiate malignant disease.

By analogy with the latent period of tumours induced in animals it is probable that tumours in man due to intramuscular imferon, were they to appear at all, would not do so until twenty or more years after injection.[1] As imferon has only been in general use for seven years, such tumours could not yet be expected.—I am, etc.,

P. E. THOMPSON HANCOCK.

Royal Marsden Hospital,
London, S.W.3.

REFERENCE

[1] Haddow, A., personal communication.

SIR,—Having read the case report by Drs. J. D. Crowley and W. J. S. Still (May 7, p. 1411) in which a metastatic carcinoma occurred at the site of iron-dextran injections, it would be of interest to know whether there are any recorded cases of metastases localizing at the site of other injections.

If so, does it not raise the question whether, in fact, injections of any description should be given to patients with carcinoma, except in the terminal phases ?—I am, etc.,

Prestatyn, N. Wales. H. O. WOOLLER.

Smoking and Personality

SIR,—Professor H. J. Eysenck and his co-authors (May 14, p. 1456) have demonstrated that smoking habits reflect personality (which need surprise nobody), and suggest that the personality differences between smokers and non-smokers are genotypically determined. This observation is certainly compatible with the theory that lung cancer and smoking habits have a common genotypic cause, but it does not, as they claim, make this theory any more reasonable. A comparison between the personalities of motor-racing drivers and tiddly-wink champions would doubtless show different ratings, probably in part genetically determined ; the death rate in car accidents of the former group would still be reduced if they stopped driving. The most reasonable explanation of the correlation between smoking and lung cancer is that carcinogenesis occurs, and none of the further studies proposed by Professor Eysenck *et al.* would serve to exclude this explanation. Only if a group of non-smokers showing the extraversion and non-rigidity of the heavy smoker were shown to suffer the same incidence of lung cancer as their smoking brethren would the tobacco manufacturers have the right to set their consciences at rest.—I am, etc.,

London, N.W.5. ANTHONY RYLE.

SIR,—Professor H. J. Eysenck and his colleagues (May 14, p. 1456) are to be congratulated on their demonstration that people who smoke tend to share certain personality characteristics. This, of course, goes a long way towards explaining the association between smoking and lung cancer and discrediting the unproved hypothesis that smoking causes lung cancer. We can now await with interest their demonstration that women who associate with men also tend to share certain personality characteristics (e.g., a liking for social life). This will, of course, help to discredit the hypothesis that there is a *causal* connexion between association with men and maternity.—I am, etc.,

Halstead, Essex. R. E. W. FISHER.

Spiritual Healing in Hospitals

SIR,—Our attention has been called to the fact that the National Federation of Spiritual Healers has been granted access to some hospitals by the management committees concerned for the purpose of treating patients.

In *The Times* of April 18 the Bishop of Lichfield stated that: "The admission of 'Spiritual Healers' to hospital wards as reported in your columns recently raises matters of considerable concern which have now been considered at a meeting of the Executive Committee of the Churches' Council of Healing. This Council is the official representative body of both the medical profession and of the Christian Communions in England, Scotland, Wales, and Ireland, which are associated with the British Council of Churches. The medical profession is represented on it by doctors appointed by the British Medical Association, the Royal College of Physicians, the Royal College of Surgeons, the Royal College of Obstetricians and Gynaecologists, the Royal Medico-Psychological Association, the Society of Medical Officers of Health, and the College of General Practitioners ; the Royal College of Nursing also have representatives on our council. My purpose now is to point out that the National Federation of Spiritual Healers, which is seeking to introduce its members officially into hospitals for the purpose of spiritual healing, is not recognized by my council."

The National Federation of Spiritual Healers state that in some cases they treat patients by suggestion after the laying on of hands, and demonstrations of this technique were given by Mr. Harry Edwards at a meeting at the Royal Festival Hall on April 30. The responsibility for treatment of patients is vested in the consultants appointed by regional hospital boards and boards of governors, and it is unethical in a medical sense for doctors to "cover" unqualified practitioners. It is essential that the doctors concerned should satisfy themselves that in giving consent to members of this Federation to visit their patients they are not laying themselves open to the charge of "covering."

It is not suggested that an adherent of any faith should be debarred from receiving any visitor of their choice in a private capacity, and indeed valuable help has been afforded to many patients by their spiritual advisers. My council was unanimous in advising that members of the National Federation of Spiritual Healers should not be given special privileges, nor granted consultations on treatment with medical staff. They hope that hospital management committees who have already given their permission for official visits will reconsider their decisions.—I am, etc.,

London, W.C.2. V. COTTON CORNWALL,
President,
Regional Hospitals' Consultants and Specialists Association.

SIR,—In these days, when our minds are presumed to be illumined by education, anyone claiming to be endowed with the power of healing, spiritual or lay, exhibits an ideation no more mature than that of our primitive ancestors. When a physician, no matter how expert, puts a fractured leg in a splint, stitches and bandages a wound, or administers a suitable potion, he is not healing. At most, he can claim that, to the best of his ability, he has provided the ideal environment for the healing process. Even the patient takes no conscious part in the curing, which is effected by chemical and physiological procedures outwith the competence of his thought. These procedures, whether used for healing or

the reverse (as, for example, in the production of gastric ulcer), are controlled by an intelligence to which, by discretion or indiscretion, we can contribute no more than directive.

No longer do we fancy, as did Mesmer, that the hypnotist transfers magnetic powers from himself. It is a matter of giving the recipient's subconscious, but more efficient, mind the directives to produce anaesthesia for surgical procedures, to curb the desire for alcohol, or whatsoever may be the desiderata. Want of success is due either to ineptitude or to the directive's expectation being out of conformity with the laws of nature. No amount of wishful thinking will bring about the replacement of an amputated limb.

Such conscious mind as is most easily impressed by wonderment, as was that of the savage by the miraculous, can, by submerging itself in trance or otherwise, make the easiest pathway for the transmission of the directive to the subconscious. As the rain falls on the just and unjust alike, so the capacity to give the directive to the subconscious is attainable no more by the saint than by the charlatan, and is further dependent on the receptivity of the one to whom it is offered.

The process of healing is no more a spiritual matter than is the digestion of food, both of which are accomplished by the same intelligence which controls the activities of the body cells as much in one circumstance as in the other. Any religious sect that strives to make it so will achieve no more than place itself in the same category as the ancient magician or his modern equivalent, the medicine man of the savage.—I am, etc.,

Glasgow, S.3. W. MELVILLE CHRISTIE

SIR,—Mr. Harry Edwards made available to me all the case material he thought useful in my investigation of paranormal healing.[1] I used the term "paranormal" to include the various qualifications adopted by different workers—divine, spirit, spiritual, faith, as well as the Delawarr camera-complex, etc. We met and had much correspondence about his cures, and he knows that I did in every case try to obtain, often unsuccessfully, medical histories; the patients for whom it was possible to arrange it were re-examined at hospital by the physicians and surgeons in whose care they had been before Mr. Edwards's healing intervention. He knows, too, that I was invited to present my findings to the B.M.A. Subcommittee and to the Archbishop's Commission.

Has he forgotten this (May 14, p. 1503) or does he think that my investigation was not bona fide, or that I was not "scientifically trained"—or neither; or does he think that you, Sir, do not edit contributions to your journal?—I am, etc.,

London, W.1. LOUIS ROSE.

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[1] Rose, L., *Brit. med. J.*, 1954, **2**, 1329.

Masks or Silence

SIR,—I should like to support Sir Reginald Watson-Jones's views (May 14, p. 1501) on this matter, especially in regard to the use in the operation theatre of efficient masks. Many which one sees in use to-day are ineffective and dangerous. Masks may be classified as either filters or deviators. Filters are rarely effective; the late Sir Hugh Cairns told me of an experiment he once performed on himself when he had a streptococcal infection in his throat; he found that he was able to infect the culture medium in a Petrie dish through many layers of gauze tied over his mouth and nose. On the other hand, deviators which are impervious (a piece of cellophane, cardboard, tin foil, or thin sheet-metal lying inside the face-piece) force the wearer's expired air backwards behind the ears and away from the operation field, and are so effective that the late W. Cone, of the Neurological Institute in Montreal, even when he had a heavy cold, was able to operate in one. Its efficiency had been further improved by attaching a suction apparatus to it. Ever afterwards Cone used suction with an impervious mask, and found also that it improved his comfort when operating. It will be conceded that no more vigorous test of effective asepsis can be found than a long intracranial operation lasting perhaps several hours. I would make a plea for the use of effective deviators covering the face and nose and the abolition of filter masks, the flimsy cotton troughs or the layers of gauze which one still occasionally sees and which should be regarded as whited sepulchres.—I am, etc.,

The Surgical Unit,
The Royal Infirmary, Cardiff. LAMBERT ROGERS.

SIR,—I should be grateful if I might write in support of Sir Reginald Watson-Jones's letter (May 14, p. 1501). It seems that it is easier in human affairs to attain perfection than to maintain it. Our masters Sir William Arbuthnot Lane and Lord Moynihan achieved something like perfection in aseptic technique and virtually abolished septic infection of clean wounds from their operating theatres. Those who follow the same technique to-day find that infection of a clean wound scarcely ever happens. No doubt many of the surgeons using this technique harbour staphylococci in their noses, throats, or perineums, either continuously or intermittently, especially during the winter months, but this has proved irrelevant, because the use of such meticulous technique over a period of many years has in fact demonstrated that such organisms have been excluded from clean wounds.

The present tendency to return to chemicals or antibiotics is to return to the Listerian principle, and would only be justifiable if the aseptic principle had failed. It is not, however, the principle of asepsis which is failing, but its application. A stand taken by a leader of surgery such as Sir Reginald Watson-Jones has been long awaited and should be heartily applauded.—I am, etc.,

Black Notley Hospital,
Braintree, Essex. M. C. WILKINSON.

Staphylococcal Invasion of Pulmonary Infarcts

SIR,—We read with interest the report on staphylococcal invasion of pulmonary infarcts by Drs. B. A. Elliott, G. A. Gresham, and D. N. Phear (April 30, p. 1320). That this is a considerable hazard is emphasized by the following case:

The patient, a lady of 49 with a past history of peptic ulcer in 1947, was admitted to hospital in January of this year with left deep-calf-vein thrombosis, right-sided chest pain, and shortness of breath. Pulmonary infarction was diagnosed and confirmed radiologically. Two days later her right leg was similarly affected. She was treated with penicillin and streptomycin for six days. Anticoagulants had been started, but were discontinued in view of her history of peptic ulceration.

Two weeks after admission there was again sudden chest pain with acute breathlessness, and cardiographic changes consistent with massive pulmonary embolism were noted. At that stage bilateral femoral-vein ligation distal to the

profunda was performed and anticoagulants were resumed, but three days later she had another acute episode of pleuritic pain, this time in the left upper chest, accompanied by haemoptysis. This was undoubtedly yet another pulmonary infarct, and ten days later a troublesome cough developed with copious purulent blood-stained sputum and high fever (T. 104° F.—40° C.). A chest radiograph showed a large consolidated area in the left upper zone, which very soon broke down into an extensive multilocular abscess. Coagulase-positive staphylococci repeatedly cultured from the sputum were at first sensitive to chloramphenicol, erythromycin, and novobiocin, but following treatment with chloramphenicol and erythromycin were reported to be resistant to all the usual antibiotics. They remained sensitive to novobiocin and were also sensitive to vancomycin.

She was now desperately ill. Intravenous vancomycin had to be discontinued after five days owing to thrombophlebitis at each successive site. Intensive physiotherapy was begun at the same time and radiologically the abscess was somewhat smaller, though converted into one large cavity. Further sputum reports appeared now to suggest partial sensitivity to erythromycin, and she was treated for ten days with erythromycin and novobiocin, but the latter drug caused persistent vomiting and chloramphenicol was resumed, as by this time her organisms were reported to be again sensitive to it. The lung abscess continued to improve slowly, but three months from the start of her illness there is still considerable consolidation in the left upper zone, and the cavity is not yet closed.

An interesting feature of the case is that two separate strains of staphylococci have now been isolated from her sputum: phage-type 80, sensitive to chloramphenicol but resistant to erythromycin, and phage-type 83, resistant to chloramphenicol but sensitive to erythromycin. This may explain some of the seemingly contradictory laboratory reports previously received.

Pulmonary infarction has always been a most serious event, presaging a possibly fatal massive embolus. It now seems that we must regard a pulmonary infarct as fraught with danger in its own right. What should or can be done? It seems inescapable that, at the least, every attempt must be made immediately to isolate these patients from hospital staphylococci.—We are, etc.,

A. J. KARLISH.
WAVERLEY.

Royal Berkshire Hospital, Reading.

Unilateral Emphysema

SIR,—We had hoped that the use of this term "unilateral emphysema" (Dr. R. F. Fouché *et al.*, April 30, p. 1312) in those patients who were found to have unilateral transradiancy of one lung had been abandoned. There is little evidence that the transradiancy is due to emphysema, and the affected part of the lung is characteristically smaller rather than larger than normal.

We have shown,[1] in a study of 13 cases, that if an angiocardiogram is done the pulmonary artery supplying the affected area is always small. The whole vessel may be involved, or only the lobar branches.[2] We have also noted that the artery on the opposite side is unusually large in these cases. Bronchospirometry showed that, although ventilation on the affected side was diminished, the oxygen uptake was disproportionately lessened, as might be expected with a poor arterial blood supply.

We believe that the radiological appearances in patients who present with abnormal unilateral radiolucency are due to hypoplasia of the whole or part of the pulmonary artery. Whether this hypoplasia is a primary or a secondary manifestation remains an open question. On the one hand many of the reported cases have a history of previous respiratory infection; on the other, the anomaly has been seen in association with a variety of congenital cardiac lesions, and it may be that the pulmonary infections are secondary to the arterial abnormality.—We are, etc.,

J. R. BELCHER.
L. H. CAPEL.
J. N. PATTINSON.
J. SMART.

London Chest Hospital, E.2.

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2 —— Capel, L., Pattinson, J. N., and Smart, J., *Brit. J. Dis. Chest*, 1959, **53**, 253.

Rod and Serpent

SIR,—The "Rod and Serpent" is, of course, the universal emblem of the medical services the world over, and I had always understood that the inmates of old Aesculapius's snake pits were harmless creatures trained to heal wounds and sores by licking them with their forked tongues.

A year or so ago a visitor to the R.A.M.C. Museum propounded a theory that the rod was not for the purpose of stirring up the snakes and extracting them, but was, in fact, a mirror on a long handle which, held before the serpent, prompted him to spit out his venom at his supposed aggressor. This was then collected and used for therapeutic purposes.

I must confess that I had dismissed this as a fanciful theory until I recently received a copy of *Revue Internationale des Services de Santé des Armées de Terre, de Mer et de l'Air*, and sure enough on the cover of this we find the snake eyeing resentfully his own reflection. I notice that there is no hint of this in Eric Gill's famous device which appears on the cover of the *Journal*, and presumably he went into things pretty thoroughly. Perhaps one of your more erudite readers can throw further light on the subject.—I am, etc.,

R.A.M.C. Historical Museum, Church-Crookham, Hants. R. E. BARNSLEY.

Is Trichomonal Infestation Venereal?

SIR,—I should like to comment on some of the points made in the letters from Dr. L. Watt and Professor H. C. McLaren (May 14, pp. 1502–3). *Trichomonas vaginalis* infection is not a legally defined venereal disease in this country, but, if it is accepted that it is usually sexually transmitted, then by logical definition it is a disease which results from venery. Thus, as far as married couples are concerned, the infection has resulted from at least one premarital or extramarital sex contact. Naturally this is sometimes not admitted, as is the case with marital partners who have gonorrhoea.

Dr. Watt supports his argument that trichomonas infection is not due to promiscuity by quoting cases reported in elderly matrons and in virgins. When the trichomonas is found in post-menopausal women it has usually been present for many years, and there is no reason to think that it was not originally sexually transmitted. In virgins—i.e., girls with the hymen intact—the trichomonas is probably transmitted by male genital contact without penetration. Careful and tactful questioning may reveal this fact. I have also seen a virgin with gonococcal urethritis who gave a similar history. This does not imply that the *T. vaginalis* is *never* accidentally transmitted by inanimate objects; the same is true of gonorrhoea or syphilis. I agree that explaining to patients about all types of non-gonococcal genital infections needs a great deal of tact, but I do not believe it can be done by ignoring the true facts.

When a female patient with vaginal discharge is referred to hospital it is essential that smears and cultures for the gonococcus should be included in the tests taken: this does not always happen in gynaecological out-patients; nor are women normally asked about recent sex contacts, so that these men may be examined if necessary. I agree that the best answer is the diagnostic clinic for patients of both sexes organized by the venereologist and his staff alone or in conjunction with the gynaecologist. This type of clinic is already in existence at some hospitals, but, until it is more widely available, for the reasons stated above I think that patients with trichomonas infection can be dealt with better in the venereal-disease clinics than in gynaecological or antenatal out-patients as Professor McLaren suggests. I hope, however, that consultants in both specialties will co-operate in the future to make diagnostic clinics available in all large hospitals.—I am, etc.,

Lydia Department,
St. Thomas' Hospital,
London, S.E.1. C. S. NICOL.

SIR,—The difficulties attached to seeing in venereal disease clinics patients who are not promiscuous have long been recognized by venereologists, and were very ably discussed by Dr. L. Watt in respect of patients infected with *Trichomonas vaginalis* (May 14, p. 1502). The mental distress suffered is seen most acutely in pregnant women who are referred for investigation and treatment following the application of routine serological tests in pregnancy and in the elderly female patient with late syphilis. It arises also in the wives of cases of non-specific urethritis which include *T. vaginalis* infestation, and results in a natural reluctance on the part of the husband to ask his wife to attend for investigation.

The acceptance by gynaecologists of *T. vaginalis* infestation as a condition likely to affect both sexual partners merely brings to general light these difficulties. The male patient with urethritis, gonococcal or non-gonococcal (including *T. vaginalis* infestation), has no alternative but to attend the venereal disease clinic, and the experience of the venereologist in investigating and treating urethritis would appear to qualify him for the continued treatment of *T. vaginalis* infestation in the male. It seems illogical to suggest *T. vaginalis* infestation associated with a urethral discharge should be treated by the venereologist, whereas *T. vaginalis* infestation not associated with discharge should be treated by the gynaecologist. Women with *T. vaginalis* infestation are seen by gynaecologists and venereologists. The treatment of such infection is an important aspect of the work of the female venereal disease clinic, as is demonstrated by the fact that at Liverpool Royal Infirmary in 1958 *T. vaginalis* was found in 67% of women suffering from gonorrhoea and in 22% of women treated for non-gonococcal conditions. Either is therefore suitably qualified to treat cases, the bias possibly being with the venereologist, in that co-operation in treating male and female partners is easier within one department rather than between two departments.

As a venereologist I deplore the ignorance which stigmatizes all patients, innocent and guilty alike, who attend venereal disease clinics, but that it exists cannot be ignored. Eventually education of the public and of some members of the medical and nursing professions should abolish this attitude, but until this is achieved interim measures should be vigorously pursued, and the responsibility rests with the venereologist.

At Liverpool Royal Infirmary for the past twenty years a "serological" clinic has been held in the medical out-patient department for the treatment of cases of congenital and late syphilis referred from the medical and surgical wards, the Eye Hospital, the Ear, Nose, and Throat Hospital, and, more recently, from the antenatal clinics. This has alleviated a tremendous amount of mental suffering, as it is possible to withhold from the elderly female patient knowledge which might cause her to doubt her husband's early moral rectitude, and has sugared the pill of the young pregnant woman from all walks of life who must be told the diagnosis. In September, 1957, a "non-specific" clinic was opened in the gynaecological department. This was primarily for the investigation and treatment of wives of men with non-specific urethritis, including *T. vaginalis* urethritis, and it has proved of great value in reassuring wives about their husband's attendance at the venereal disease clinic. It has also been useful for seeing cases of non-specific vulvovaginitis in children and for routine tests in pregnancy in any girls whom the welfare officers are reluctant to send to the venereal disease clinic. Both clinics are run by the medical, nursing, and welfare staff of the venereal disease department, who provide their own equipment. If it is agreed, as suggested by Dr. R. D. Catterall and Dr. C. S. Nicol (April 16, p. 1177), that venereologists can most suitably deal with cases of *T. vaginalis* infestation, it is suggested that female cases can be seen in such clinics as the Liverpool Royal Infirmary "non-specific" clinic and male cases in a similar clinic held in the genito-urinary department or in the gynaecological department, as suggested by Professor H. C. McLaren (May 14, p. 1503).—I am, etc.,

Liverpool Royal Infirmary,
Liverpool, 3. ELISABETH REES.

Allergic Response to Hyaluronidase

SIR,—Allergic reactions to hyaluronidase are rare, and H. Kendall[1] and E. J. Holborow and M. K. Keech[2] reported instances of sensitivity after repeated injections. Protein impurities have been implicated. The following case report describes a severe anaphylactic reaction following administration of hyaluronidase in combination with prednisolone-21-phosphate ("codesol") and hydrocortisone acetate.

Case Report.—A male patient aged 27 years was seen complaining of pain in the right lower intercostal muscles, which was diagnosed as "intercostal fibrositis." There was a previous history of pulmonary tuberculosis, but no evidence of recent activity. Conservative measures proved unhelpful, and an attempt to relieve the intense pain was made by infiltrating the affected muscles with 1 ml. of prednisolone-21-phosphate, 1 ml. of hydrocortisone acetate, and 1,500 units of hyaluronidase in a single injection.

Relief of pain was almost immediate, but twenty minutes later he was in a collapsed state, respiration was rapid, and marked bronchospasm was present. The face, lips, and tongue were swollen, and a generalized urticuria was apparent. Retrosternal and abdominal pain was present, and he complained of discomfort in elbow, wrist, knees, and ankle-joints.

One millilitre of 1:1,000 adrenaline was slowly administered subcutaneously, and 10 mg. of chlorpheniramine maleate ("piriton") was given intravenously, and a further 10 mg. intramuscularly. Recovery was slow; however, the major symptoms cleared after forty minutes. Severe urticarial itch persisted, but it was interesting to note that there was no local reaction at the site of the infiltration. He was given further "piriton" orally, 4 mg. q.i.d. Recovery was complete within 4 hours, and the pain due to the myofibrositis had cleared completely.

One week later he was skin-tested, the solutions being diluted 1:100 with sterile normal saline, and 0.01 ml. given intradermally. The results were as shown below.

Control—Normal saline	No reaction. Weal, 2 mm.
Prednisolone-21 phosphate Hydrocortisone acetate Hyaluronidase	Moderate reaction. Weal, 5 mm. Erythema present. Slight itch
Prednisolone-21 phosphate Hyaluronidase	Moderate reaction. Weal, 5 mm. Erythema present. Slight itch
Hydrocortisone acetate Hyaluronidase	More marked reaction. Weal, 8 mm. Large patch of erythema. Marked itch
Hyaluronidase ..	Strong reaction. Weal, 12 mm., with pseudopodia present. Marked erythema. Intense itch

It was therefore decided that the reaction described was due to the hyaluronidase alone. A similar case was described by K. Barber.[3] The present reaction was probably modified by the added corticosteroid.

In view of the widespread use of hyaluronidase, especially in obstetrics and casualty departments, the possibility of an anaphylactic reaction should be remembered. It is suggested that skin-testing to hyaluronidase should be tried, particularly before any repeated course of this substance. In the present case, steroids given with hyaluronidase did not prevent a sensitivity reaction—I am, etc.,

Wombwell, Yorks. NORMAN MACLENNAN PIERCY.

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2 Holborow, E. J., and Keech, M. K., ibid., 1951, **2**, 1173.
3 Barber, K., ibid., 1957, **1**, 166.

Sympatho-adrenal Activity in Thyrotoxicosis

SIR,—Some clinical signs of thyrotoxicosis, such as finger tremor, tachycardia, elevated blood-pressure, nervousness, etc., can be caused by the sensitization of the effector cells by the thyroid hormones for the excitatory action of noradrenaline and adrenaline. Increased sympatho-adrenal activity need not therefore be involved in thyrotoxicosis. However, Spinks and Burn[1] found that in rabbits thyroxine inhibited the enzyme monoamine oxidase. This would result in diminished destruction and accumulation of the amines. In patients with thyrotoxicosis a strikingly increased urinary excretion of adrenaline has been described by Diller and Kilpatrick[2]; in hypothyroidism the excretion was diminished. Holtz and his co-workers[3] found that thyroxine did not alter, or even increase, the content of amine oxidase in the liver of rats, guinea-pigs, and rabbits. The enzyme activity of dopa-decarboxylase, on the other hand, was diminished by thyroxine. This would result in a normal or increased destruction and a decreased biosynthesis of the amines.

We have investigated the urinary excretion of noradrenaline and adrenaline in 20 cases of thyrotoxicosis (method of von Euler and Floding[4]). We found that the excretion of adrenaline was within the normal range in all cases. The excretion of noradrenaline was either normal or, in eight cases, even low. These low values increased along with the clinical improvement during treatment, but remained within the normal limits. Three patients with hypothyroidism eliminated sometimes strikingly increased quantities of noradrenaline. Preliminary investigations of the excretion of phenolic acids in the urine of two patients with thyrotoxicosis gave no hint of an increased excretion of catechol amine metabolites. These results give no support to the assumption of an increased endogenous production of adrenaline and/or noradrenaline in thyrotoxicosis.—We are, etc.,

H. J. KUSCHKE.
H. WERNZE.
G. BECKER.

Medizinische Univ.-Klinik, Würzburg, Germany.

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American Examination for Foreign Medical Graduates

SIR,—I would like to draw your attention to certain recent regulations set up by the Educational Council for Foreign Medical Graduates of the American Medical Association. These regulations present a definite retrograde step in the co-operation and mutual growth of Anglo-American medicine. Details of the regulations, which will come into force on July 1, can be found in the *Journal of the American Medical Association*.[1 2]

In brief, it is required that any doctor who is not a graduate of a medical school in the United States, Canada, or Puerto Rico must sit an examination to evaluate his knowledge of medicine and command of the English language. Without passing this examination one cannot be accepted by any university or hospital in any capacity—viz., intern, resident, or fellow. This effectively places an obstacle in the way of the young British doctor in training who would like to broaden his outlook by spending a year in the different climate of medicine of the United States. Please note that this examination is quite separate and distinct from the various State licensing examinations required before one can practise outside of a hospital.

One can understand why the Americans have felt it necessary to institute this examination, but surely a British doctor should be exempted as is a Canadian. The actual examination, which incidentally costs $25 and may be taken in London, is not difficult, consisting of 360 multiple-choice questions mainly on medicine. However, I feel it quite unnecessary and rather humiliating that a British graduate should have to be examined at all, and especially on his command of the English (? American) language. I understand that an American graduate can take a year's training in Britain without any similar nonsense. Surely this ought to be reciprocal. I am all for more intercourse between British and

American Medicine, and I feel that this new obstacle should be rapidly demolished.—I am, etc.,

Montreal General Hospital. W. GERALD WALLIS.

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[2] Ibid., 1960, **172**, 1045.

Routine Examinations for Neoplasms

SIR,—Most of us know of patients whose chances of survival would have been good instead of hopeless had existing technical knowledge been used at the right time in determining whether they had some common neoplastic disease. I am prompted to write this letter because a patient of mine, aged 47, who had only minimal symptoms for two months, was found to have carcinoma of the cervix uteri "too extensive for radium." The extension of routine examination of persons at risk to certain common neoplasms is urgently needed where such examinations are simple and safe. Already mass radiography plays a useful role, and in certain industries, I understand, routine examinations are made to exclude occupational cancers.

This country lags far behind the U.S.S.R. and U.S.A. in routine examinations for carcinoma of the uterus, whose scope has been much increased by recent advances in cytology. An up-to-date scheme based on cytological examination of vaginal smears should make routine examinations a simple matter for clinician and patient, though requiring considerable numbers of specially trained laboratory technicians. It would take time and money to train the technicians and to run the scheme, but I think it is time that someone asserted that we can afford such things. In a few localities, I understand, some such schemes are already in operation, but what is needed is central encouragement to their establishment in all centres of population, using existing simple techniques of examination pending the training of the necessary technicians.—I am, etc.,

Brighton, 6. R. S. SAXTON.

Nitrogen Mustard Therapy

SIR,—Dr. B. H. Bass in his article on the use of nitrogen mustard in the palliation of lung cancers (February 27, p. 617) has stated that the phenothiazine group of drugs is of very little value in the prevention of nausea and vomiting during treatment with nitrogen mustard. One of the phenothiazine derivatives, prochlorperazine, is a very effective anti-emetic agent. It stops nausea and vomiting in radiation sickness, pregnancy, and motion sickness.

During the course of a few months I have observed eight patients with malignant disease treated palliatively with nitrogen mustard. After a test dose, the usual dose employed was 0.4 mg./kg. body-weight. This was divided into four doses and given on successive nights or in the mornings after making sure that the patient had starved a few hours before. Twelve hours before the injection of nitrogen mustard was given a 10-mg. "spansule" of long-acting prochlorperazine ("compazine") was given orally to the patient. About 15 minutes to half an hour before the nitrogen mustard was administered into the rubber tube of the intravenous infusion of glucose in water, another 10-mg. dose of compazine was given intramuscularly. Sometimes a combination of compazine with an antihistaminic (chlorpheniramine maleate) was used. With this prophylactic anti-emetic therapy the incidence of nausea and vomiting was very little in the patients receiving nitrogen mustard. Only two patients developed mild epigastric discomfort and nausea, but they did not have vomiting. Of course, all the phenothiazine derivatives are liable to produce side-effects like Parkinsonism (described by Drs. E. R. Bickerstaff and E. Jacoby at p. 647 of your same issue), jaundice, allergic reactions, and agranulocytosis, but if they are used cautiously they are of extreme benefit in the prophylaxis of nausea and vomiting during nitrogen mustard or radiation therapy.—I am, etc.,

Knickerbocker Hospital, New York. P. NARASIMHAN.

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Obesity in Childhood

SIR,—Dr. F. G. A. Bateman's reply (April 30, p. 1366) to my letter (March 26, p. 965) appears to be evasive. He establishes that "preludin" (phenmetrazine) is eight times weaker than the amphetamines, and the statistics he offers on the controlled use of preludin shows that this drug has some value. I have not raised nor did I dispute this, I am solely concerned about the uncontrolled use and unrestricted sale of preludin. For almost ten years and in all countries this drug could be bought freely. Slowly international control is being brought about, and by this alone it can be considered a dangerous drug.

I have, it appears, to labour the issue. In addition to suppressing appetite, preludin, like the amphetamines, is a cerebral stimulant. For depression, feelings of inadequacy, or just for the "kicks" the world sales must have been enormous, and the press in our own country has recently described bizarre and criminal behaviour in association with the use of this drug. The clinical picture of paranoic attitudes and hallucinations I wrote of I have seen for myself. Preludin is potentially addictive and toxic, and unfortunately it is still being sold freely in other countries; it was controlled only this month here. Considering its actions and the types of disability it would appear to help, I repeat that the free sale of this drug in the last decade has been both enormous and disastrous.—I am, etc.,

Cardross, Dunbartonshire. PHILIP M. ELLISON.

"Lipostabil"

SIR,—I have read the various comments on lipostabil that have appeared in your columns with very great interest. Dr. L. G. G. Davies and Miss Lesley Murdoch investigated 10 cases of ischaemic heart disease, but their report (October 3, 1959, p. 619) gives details of only eight. Two cases belonged to the group of xanthomatosis with hypercholesterolaemia, in which it is notoriously difficult to cause a reduction of the cholesterol level and an improvement of the xanthomata by medical means. Dr. T. C. Butler *et al.* (January 23, p. 276) were unable to obtain any satisfactory effects on cholesterol, lecithin, fibrinolysis, and lipoproteins in 50 cases of ischaemic heart disease. Unfortunately they gave no details and their tabulated summary does not show variations of the individual values during treatment.

I should be grateful if you would permit me to call attention to the results obtained by several research groups in Western Germany; university clinics in Marburg (Schettler[1]), in Hamburg (Küchmeister[2]), in Köln (Leupold[3]), in Erlangen (Schön[4]), in Frankfurt am Main (Schrade *et al.*[5–8]), in Heidelberg (Lasch *et al.*[9]), in addition to medical clinics in Aix-la-Chapelle (Schroeder[10]) and in Heidelberg (Knüchel[11–13]). There are also reports from Italy,[14 15] and from Switzerland.[16 17] In all these centres patients with coronary heart disease have been treated successfully with lipostabil during the last 7 years, but the very nature of the disease excludes the possibility of curing. In addition to clinical improvement, there was significant reduction of serum cholesterol, normalization of the cholesterol-phospholipid ratio, improvement of the so-called atherogenic index, and of the lipoprotein pattern. These, as well as effects on coagulation factors, lay well outside the possibility of coincidence. Further, lipostabil given intravenously produces a clearing effect on lipaemic serum and a change in the unesterified fatty acids of the serum. These results obtained with lipostabil should be considered in relation to the results published by Dr. Davies and Miss Murdoch, and by the Tasmanian workers (Dr. Butler and his colleagues).—I am, etc.,

Stuttgart, West Germany. G. SCHETTLER.

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Laissez-faire Antenatal Care

SIR,—With reference to Dr. Hamish Nicol's letter (May 14, p. 1504), one is taught in medical school and hospital antenatal work to examine patients routinely every four weeks until the 28th week, fortnightly until the 36th week, and then weekly until birth. At each attendance the blood-pressure and urine should be tested and the patient weighed. An abdominal palpation should be performed frequently, if not at every attendance, and at least one pelvic examination. The haemoglobin and blood group should be ascertained and an interest should be shown in the patient's progress and well-being.

Many of us manage to continue this regime in general practice, not to mention the further supervision during labour and the lying-in period. We could diagnose pregnancy across the consulting-room desk, tell the mother it is a perfectly normal process and to trot along to see the midwife at the clinic. So long as we ensure Form E.C.24 is signed we collect seven guineas just the same. Only the occasional expectant mother will suffer from the lack of supervision, but she is precisely the person whose condition antenatal work is designed to remedy in good time. Surely the N.H.S. payment is far too small for the first kind of service and far too much for the second.—I am, etc.,

Caterham. BRIAN HEBER.

Mothers' Preference in Confinement

SIR,—In an attempt to resolve the misunderstanding which has subsisted between us in our comments (March 19, p. 879) and Drs. I. Gordon and T. F. Elias-Jones in their report (January 2, p. 52) and in their reply (April 30, p. 1365) to our letter, we should like to present the following somewhat analogous hypothetical situation in the field of market research.

Suppose that nearly all washing machines are sold with a packet of a detergent of the kind A, with a definite recommendation to use it and perhaps to continue to use the same kind; but that A has some characteristics (such as high cost or peculiar smell or a tendency to cause dermatitis) which *some* (x%, say) users find, after trying it, to be unpleasant or intolerable. Suppose that there is an alternative detergent, of the kind B, which these users proceed to try and, in the great majority of cases, do adopt. Then a survey of the preferences between A and B, restricted to those who have used both A and B in their machines, would be very likely to show a high percentage (y, say) preferring B. This high rate of preference for B would have no necessary connexion with the preferences of the unvarying users of A, who might be well satisfied with it and have perfectly sound objections to B. Moreover, there may be no correspondence between the percentage prevalence of any of the positive or negative reasons for preferring A or B, among those who have tried both, and the extent to which these reasons would influence the constant users of A or B. For example, trouble with dermatitis might be very common in those who have tried both A and B, but insignificant for those who have tried only A.

As we understand Drs. Gordon and Elias-Jones, they claim that a large value for y would be evidence that many of the constant users of A could, with advantage, change to B. (The analogy is obviously inexact, but one might equate the users of the washing machines to the mothers, each packet of detergent to a confinement, and A and B to hospital and home confinements, respectively.) Our main comment was equivalent to pointing out that y should be expected to be large, inevitably, and that if the opinions of the constant users of A (or B) are to be found, they must be sought more directly. (A random sample of 100 multiparous mothers could provide some very useful information.) The value of y appears to be irrelevant, except in combination with other information. If x is small, the overall percentage preferring B may be very much less than y.

As regards proving the Cranbrook Report to be wrong in implying that only about 10 to 20% of mothers prefer home confinements, the Ilford report (January 2, p. 52) has shown that in 17% (269 out of 1,552) of their confinements a hospital bed was not needed, in the sense that the mother was experiencing her second or later confinement and subsequently expressed a retrospective preference for home confinements. Using the estimates in our table (March 19, p. 880), we can add about another 9%, consisting of 113 primigravidae who had their babies at home and 25 multigravidae who had all their confinements at home up to the time of the survey, assuming as an approximation that all these home confinements were by choice. It therefore seems that

the information obtainable from the Ilford investigation is not greatly at variance with this aspect of the Cranbrook Report.—We are, etc.,

M. C. K. TWEEDIE.
JOYCE K. TWEEDIE.

Liverpool, 19.

Truth about Psycho-analysis

SIR,—In a letter (April 2, p. 1051) objecting to Professor H. J. Eysenck's criticisms of psycho-analysis in the January *Reader's Digest*, Dr. William H. Shepley suggests that if Professor Eysenck had had practical experience in the treatment of neurotic patients he would not have come to his conclusions. This expresses an attitude characteristic of psycho-analytically oriented psychotherapists, who, while rejecting statistical findings with allegations of lack of scientific rigor, place great value on the testimony of imprecise and not impartial personal impressions.

Dr. Shepley asserts, on the strength of his experience, that "orthodox methods" afford only temporary palliation of neurotic suffering, while psycho-analysis alone aims at attaining "permanent freedom from all further trouble." However, statistical studies have consistently shown that when "orthodox methods" result in apparent recovery or marked improvement of neurotic illness, such improvement is almost invariably lasting. For example, in a 5–15-year follow-up study, Hamilton, Varney, and Wall[1] found evidence of relapse in only 1 of 67 female patients who had been greatly improved by the use of these methods. Such findings, flatly contradicting psycho-analytic predictions, should lead psycho-analysts to question their theory and not, as usual, dodge the issue by saying that there must be something wrong with the findings.

The statistics to which Professor Eysenck refers indicate that psycho-analytic therapy yields about the same proportion of highly favourable outcomes as "orthodox methods" — usually about 50%. This suggests that a common process is the real basis of improvement in both groups. Recent work[2] based on modern experimental psychology has produced evidence suggesting that the common process is reciprocal inhibition of anxiety responses by emotions that are physiologically antagonistic to anxiety and that are aroused by factors in the interview situation. Repeated inhibitions of anxiety diminish the strength of the neurotic response habit, eventually eliminating it. Unfortunately, this anxiety-inhibiting process occurs spontaneously in only some patients. But methods have been devised by which inhibition of anxiety responses can be brought about deliberately, and with the use of these methods about 90% of neurotic patients have been apparently cured or much improved in a median number of 22 therapeutic sessions.[2,3]—I am, etc.,

JOSEPH WOLPE.

University of Virginia, Charlottesville.

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Students' Acceptance of Psychiatry

SIR,—I was interested in Dr. H. B. Kidd's passionate defence of determinism (April 16, p. 1205). I am in sympathy with him in regarding it as a useful assumption in dealing with many transgressors against the law, but surely it cannot seriously be defended as a rational doctrine. Dr. Kidd submits that, "given complete knowledge of the facts, we should know precisely how a person will, or, indeed, must, behave." But how can we talk of having such knowledge if the act of knowing is an inevitable result of preceding physico-chemical processes?

It is a well-known philosophical dilemma that both determinism and free will are apparently irrational. The nature of causality and its alternatives is something which we do not yet understand. The extrasensory perception experiments of Rhine and Soal, culminating in the statistically significant results for precognition and psychokinesis, have shaken the foundations of our concept of causality. Jung[1] went so far as to say, "The Rhine experiments have demonstrated that space and time, and hence causality, are factors that can be eliminated, with the result that acausal phenomena, otherwise called miracles, appear possible."

Surely we should at least remain humble about our knowledge of psychic processes. By all means let us assume that many criminals and psychopaths are unable to control their behaviour, but do not let us go beyond this into an unquestioning acceptance of scientific determinism. If we do, then we must assume that the psychiatrists who are treating these unfortunates are also unable to control their actions and that their therapy is simply the result of predetermined physiological processes.—I am, etc.,

GORDON P. WALLACE.

Maidstone.

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Psychogenic Disorders in Children

SIR,—In our letter (March 26, p. 968) we used the words "*treat* psychological illness": by this we meant, in effect, giving psychotherapy to emotionally disturbed children. We did not mean "management of common behaviour problems," which we agree with Professor R. S. Illingworth (April 9, p. 1131) it is the job of any paediatrician to undertake to the best of his ability.

We would like to make amends for any lack of clarity in the words "psychological illness" by giving as examples anxiety states, arrest of emotional development, withdrawal, of all degrees, and conditions in which a parental neurosis is an important factor. The treatment of such usually involves arranging a setting and entering into a relationship with the child or parent in which they will reveal things about themselves which they would not do under more superficial management. It means, moreover, the interpretation of what is revealed and dealing with any secondary emotional disturbances resulting. The word treatment can, of course, embrace a great deal, and might include even the run of dry beds which an enuretic child frequently has in mere anticipation of going to see the specialist.

The controversy arising from Dr. John Apley and his colleagues' account of their interesting experiment in the management of psychogenic disorders in children (January 16, p. 191) is mainly round the question of how far a paediatrician (with the collaboration of a psychiatric social worker) can venture into the field which is generally understood as psychiatry. Clearly no line can even be arbitrarily drawn. Collaboration between paediatricians and psychiatrists is very important, and it

was in support of Dr. Apley's move in this direction that we described our own experiment.—We are, etc.,

EDITH M. BOOTH.
Aylesbury, Bucks. DERMOD MACCARTHY.

Medicine on Television

SIR,—Surely the time has come for the B.M.A. to take action against the medical rubbish—dangerous rubbish—which is being turned out by B.B.C. T.V., apparently without any thought of its effect on the masses. I refer to the "Eye on Research" programme of April 19, filmed in Australia, in which several patients suffering from various conditions, including rheumatoid arthritis, told how they were improved by cortisone treatment. I am shocked that the B.M.A. seems to take no action in restricting the showing of these unbalanced and misleading medical programmes to the viewing masses. To my mind this country is rapidly approaching the stage when we will see slot machines in the streets for blood-pressure readings, and it certainly will not be long before the patients will be telling their doctors what treatment they want for their arthritis; and, if not, why not?

In my opinion, educating the public on medical matters up to a point is a good thing, but it is of prime importance that the programme is produced or directed by someone who knows the dangers of showing detailed technical data to a completely untrained viewing audience. I am quite certain that these programmes do nothing but harm. It would be interesting to know how other G.P.s feel about this.—I am, etc.,

Ballycastle, N. Ireland. C. D. STEWART.

Fat, Calcium, and Coronary Disease

SIR,—One of the most important nutritional problems at the present moment relates to the culpability of a very high intake of animal fat—for example, butter fat—in regard to its capacity, directly or indirectly, to promote ischaemic heart disease. Now there is a certain amount of evidence that when a dietary component is ingested in excessive or in deficient amounts the occurrence and severity of stigmata appear to depend on the pattern of diet consumed. On this account, the above problem perhaps could be put more explicitly: Does a very high intake of butter fat *ipso facto* promote ischaemic heart disease, *irrespective* of the dietary setting?

Most reviews and current papers bearing on the subject appear to consider that ultimate ill-effects are inevitable. Cleave,[1–3] however, "holds that man may eat with perfect safety any fats existing in his natural environment, so long as he eats them in strict proportion to his appetite. In civilized countries there is, however, through the agency of arbitrary meals and arbitrary foodmixtures (of which ice-cream is one) a profound interference with this instinct."[4] Now population groups very suitable for throwing light on the issue under discussion are those who live to a large extent, or even exclusively, on milk. Such groups are available in Somaliland and Eritrea, nomads who subsist throughout much of the year almost entirely on milk from goats, camels, and sheep. Publications[5–7] indicate consumptions of 2½, 4, and even as much as 9 litres per diem. Very approximately (on the basis of the composition of camels' milk, 5.4% fat) these volumes provide 135, 216, and 486 g. fat, supplying about two-thirds of total calories. It is not, of course, entertained that all these people consume this type of diet all the time, but it should be possible, by selection of subjects, to investigate the health pattern of a sufficient number of habitually high consumers of milk to learn whether they do or do not display the stigmata attributed to a very high intake of milk fat. Are these people characterized by high serum cholesterol levels, occasionally severe arterial lesions, and high mortality from coronary heart disease?

Study of these people may throw light on another relevant problem. Yerushalmy and Hilleboe,[8] in their critical study of intakes of nutrients and mortality rate from coronary heart disease, have demonstrated that the best correlation prevails between animal protein intake and mortality rate. In the nomadic groups referred to, the intakes of animal protein from the volumes of milk stated are about 75, 120, and 270 g., supplying about 17% of calories. Do such high animal protein intakes by these people correlate with excessive mortality from coronary heart disease?

There is yet a further point. The contributions of calcium from the volumes cited are about 3, 5, and 11 g. per diem respectively. Is this high calcium intake innocuous or harmful? Among our local Bantu, calcium intake, serum calcium levels,[9] and intensity of aortic calcification[10] are low in comparison with corresponding data on the white population. One has thus been tempted to speculate that a low, in contrast to a high, intake of calcium, directly or indirectly, might have a retarding effect on the disease process under discussion. It may be recalled that in Britain, when the fortification of the staple bread meal with calcium salts was discussed in 1941, there was a certain amount of apprehension over the possible noxious effects of an increased calcium intake on atherosclerosis.[11]

The securing of knowledge on the metabolism and the disease pattern of such population groups, with their excessive intakes of animal fat, animal protein, and of calcium, might well provide crucial information bearing on current hypotheses on the aetiology of ischaemic heart disease.—I am, etc.,

South African Institute for Medical Research, Johannesburg. ALEXANDER R. P. WALKER.

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Diarrhoeal Diseases

SIR,—The high and increasing incidence of dysentery (leading article, April 2, p. 1034), the gastro-enteritides, and salmonelloses is truly disturbing, but I feel that both as a nation and as a profession we are guilty of hypocrisy in our attitude to these diseases. We have allowed ourselves to be hypnotized into believing the "fevers is dying" myth, and consequently are ill-equipped to deal with any epidemic. A garden is not dying simply because the hyacinths of spring are superseded by the hollyhocks of summer. If we sincerely wish to eradicate these infections surely we must adopt the approach that has already shown considerable success with tuberculosis: the present half-hearted methods are a useless waste of time, drugs, and hospital beds.

Anyone who has worked in an infectious diseases unit knows how often only the youngest and most susceptible

member of a family is referred to hospital with vomiting and diarrhoea, but on inquiry it almost invariably transpires that one or more other members are suffering also, though less acutely. It is also a heartbreaking commonplace that within a few weeks of this child being discharged home, clean, well-nourished, and infection-free, it returns as ill as before, reinfected by its carrier sibs. Surely it should be standard practice that all contacts should be isolated until cleared by bacteriological examination, or treated if infected.

The obvious place for these infections to be treated is in a fevers unit, which is usually the only place well adapted to barrier-nursing. A halt must be called to the disastrous trend to conversion of fevers hospitals for use as units for which they were not intended and are very poorly suited. I am only too well aware of the shortage of fevers nurses, though I feel this is partly due to the "fevers is dying" myth. The obvious answer is to extend the S.R.N. training course to three and a half years, of which at least six months should be spent in an infectious diseases unit. This is in any case a long-overdue step: nowadays the fevers hospital is apt to receive a large variety of general diseases whose only connexion with "fevers" is an elevated temperature; while in a general hospital trying to ensure that an infectious case is barrier-nursed by staff not trained in fevers is absolute hell.

Our first step must be to educate ourselves to realize that we must not shrug off the first few cases of diarrhoea and/or vomiting as "gastric 'flu" or a "touch of food-poisoning," sending the patient home to disseminate his organisms, with the solace of mist. kaolin. sed. or an insoluble sulphonamide. (*Sh. sonnei* is now very largely sulphonamide-resistant.) Our next step must be to teach the nursing profession that diarrhoea must be regarded as due to infection rather than aperients until proved otherwise, instead of vice versa, as at present (almost to a woman, they prefer to empty 10 bedpans a day rather than send three daily specimens of faeces to the Path. Lab.). Finally, we must teach the public that it is as antisocial to spread dysentery as to spread tuberculosis or venereal diseases. But if we are to act in time we must act now.—I am, etc.,

Hastings, Sussex. PAULA H. GOSLING.

Wound Excision

SIR,—In discussing the principles and technique of wound surgery, the recent excellent publication from the Birmingham Accident Hospital *Modern Trends in Accident Surgery and Medicine*, by Clarke, Badger, and Sevitt, very rightly condemns unnecessary wound excision, especially of skin, and emphasizes the management of wounds on biological principles. The superficial reader—and some reviewers appear to be such—may gain the impression that excision has been abandoned in wound care. This would be a pity and lead once more to the surgical disasters that occur repeatedly at the beginning of a new war as a result of forgetting the lessons learned in the last. Nothing is more regrettable in medicine than the repetition of mistakes already made, corrected, and recorded. This has been pointed out more than once by Heneage Ogilvie[2,3] and by Latta.[4]

The book takes exception to the term excision, and emphasis is laid on enlargement and decompression of the wound, both very important. Surely it is a matter of terminology. Various words have been used for intelligent and correct wound excision, and not the least common and useful is the French *débridement*: another is the English term toilet—"a rose by any other name . . ."

Yet the careful reader will note that the lessons learned in the "academies" of wound surgery established in wars are clearly reiterated. "The wound has now been widely opened and explored; dirt and foreign bodies have been removed; dead muscle and perhaps some other devitalized tissue have been excised." The importance of removing dead muscle, the ideal medium for the establishment of infection, particularly of gas gangrene, is discussed. Latta, in the article cited, states, "nothing can take the place of efficiently planned surgical toilet of a wound."

The possibility and likelihood of primary suture of civilian wounds is indicated, and the importance of using in the wounds of war nothing other than a technique of delayed primary suture, the valuable but regularly forgotten lesson of wars, is restated. The basic principles of surgery are unchanging, and this is one of them. It is an established precept, based on sound biological principles and confirmed repeatedly by experience. Certain few favoured exceptions to its use need not be mentioned here. It must remain a general standing order for the care of war wounds. The earnest cry and prayer should be that it may never be again forgotten. Learned in the Kaiser's war, forgotten in the early part of the 1939–45 war and, even later, once again in Korea, as well as recently in some of the few Suez casualties, may it never be lost sight of again.

The principles of war surgery drawn up by Heneage Ogilvie[5] as his Ten Commandments stand as ever. The fourth, "Thou shalt not excise skin," emphasizes the value of this organ in converting the open wound with all its dangers into a closed one. Such laws must regularly be brought to the notice of all concerned and enunciated, not only in the medical schools of the armed Forces but wherever surgery is taught.—I am, etc.,

Department of Anatomy,
University of Aberdeen. A. G. D. WHYTE.

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Inoculation Technique

SIR,—I have only just seen the letters on the expulsion of vaccine lymph from capillary tubes that appeared in your issue of April 30 (p. 1363). There is a very simple version of Dr. M. J. Derbyshire's device which can be bought ready-made from any chemist. Ordinary baby feeding-bottle teats without a perforation or with one fine hole serve admirably as expellers and have been used here for many years. The opened capillary is inserted into the pin-hole in the teat; the open end is occluded by the vaccinator's thumb and then gentle pressure on the sides of the teat expels the lymph on to the prepared vaccination site. One teat will serve for many vaccinations.

We cannot endorse Dr. W. H. Spoor's method of heating the capillary tube from the unopened end with a swab moistened by spirit. A spirit flame is very hot and the virus is very labile. Nor can we approve his method of swabbing the vaccination site with spirit. The official advice is to treat the site with ether or acetone, which evaporates immediately. Ordinary spirit takes longer than is generally recognized to evaporate completely, and spirit is lethal to vaccinia virus. I understand, however, that the public-health laboratories issuing vaccine lymph hold little bulbs for expelling lymph for issue to practitioners.—I am, etc.,

Smallpox Vaccine Department,
Lister Institute of Preventive Medicine,
Elstree. DOUGLAS MCCLEAN.

Congenital Dislocation of the Hip

SIR,—Mr. W. Sayle-Creer and Mr. T. G. Barlow in their interesting letter (May 7, p. 1427) have submitted a somewhat subluxated picture of the "true incidence" of the condition. It is a well-recognized fact that the incidence of breech presentations is much higher in cases of C.D.H. than in the general infant population (in my experience, seven times greater). Their letter overlooks the fact that quite a few babies are born at home and that the incidence of C.D.H. among these is, for obvious reasons, likely to be less than in those born in hospital. In my limited experience over the last 11 years the incidence of C.D.H. is three times greater in the hospital-born. The defence rests.—I am, etc.,

Wembley. R. A. STRANG.

Compulsory Treatment

SIR,—In case no one else has yet written to you, may I point out to your Legal Correspondent (May 7, p. 1430) that Section 224 of the Public Health (London) Act, 1936, was repealed by the National Assistance Act, 1948. —I am, etc.,

London, W.C.2. G. W. PIPER.

*** Our Legal Correspondent writes: *Mea culpa!* The substance of Section 224 now appears in Section 47 of the National Assistance Act, 1948, as amended by the National Assistance (Amendment) Act, 1951, where certain changes were made relating mainly to procedure and to the duration of the court order.—ED., *B.M.J.*

POINTS FROM LETTERS

Congenital Dislocation of the Hip

Dr. ELIZABETH LOEWENSTEIN-KUESTER (London, N.W.3) writes: When I was in Czechoslovakia in 1958, where there is an excellent National Health Service, I found that parents were urged to take their newborn babies at 3 or 4 months to the orthopaedic department of their local or nearest hospital to have them *x*-rayed, as the medical authorities are very much aware of the fact that all skeletal anomalies have the greatest chance to be treated with complete success during the child's first year of life. Transport and other facilities are provided and many parents make use of the scheme. I know of no figures, but it appears that the incidence of congenital dislocation of the hip is rather large. I understood that a kind of prefabricated spica is used in the treatment.

Osteoarthritis of the Hip

Dr. E. H. STRANGE (Buntingford, Herts) writes: As an elderly sufferer for some eight years with osteoarthritis of the hip I have been greatly interested in the excellent articles of Mr. John Charnley (March 19, p. 821) and Mr. P. A. King (p. 827) and your leading article (April 23, p. 1260). Osteoarthritis of the hip is a most insidious disease, and the most important point in its treatment is early diagnosis. In industry the industrial M.O. may reasonably suspect its presence when a man or woman doing repetition work over a bench complains that some movement or activity has now become noticeably uncomfortable or fatiguing. . . . When osteoarthritis of the hip is diagnosed the patient should be put upon a fairly strict regime of manipulation and corrective exercises. Above all the patient should be warned about the adductor deformity, which almost always occurs in any moderately severe case. The adductor deformity is the most embarrassing factor, after severe pain, in walking. It is produced by pain inhibiting walking correctly. In my opinion it can be staved off, delayed, or reduced by suitable manipulations and exercises. It is often produced, hastened, or increased by the use of a walking-stick. The victim of this disease usually walks with a stick on the good side, swinging the affected limb around and towards the good side, and for the sake of speed he gives up the attempt to use the affected limb properly. He should be taught to use the stick on the affected side to help that limb to act as normally as possible.

Surgery of the Hip-joint

Mrs. MARJORIE ROSS, M.C.S.P. (British Red Cross Physiotherapy Unit, Bletchley), writes: The recent articles on surgery of the hip-joint (March 19, pp. 821 and 827) have been of enormous interest to physiotherapists, who frequently have to help the patient to bridge the gap between the immediate post-operative situation and the adaptation of this situation to everyday life. It is in this sphere, surely, that the physiotherapist can be most usefully employed. Common-sense principles applied to helping the handicapped to live with reasonable comfort provide a most worthwhile field of work, and the letter from Dr. W. K. Dunscombe (May 7, p. 1427) stresses the need for this work.

Inoculation Technique

Dr. H. S. C. WIGHT (Duffield, Derbyshire) writes: I read Professor Thomas Anderson's letter (March 19, p. 882) with astonishment, and I waited with interest to see how general practitioners would answer his charges. . . . I started inoculating my patients against polio in September, 1957, and between then and now I reckon that I have carried out 543 such injections. For the most part I, too, have used the technique which Professor Anderson says is so dangerous. In this same period I have attended three patients with hepatitis, none of whom had had a polio inoculation. There have been no cases of hepatitis amongst the inoculated patients. It is all very well for Professor J. W. Howie (April 2, p. 1055) to say that there should be a separate syringe and needle for each patient, and to quote, in support, the bigwigs of the Medical Research Council. This is easy enough to carry out in large clinics, but in general practice, with relatively small surgery accommodation—often the branch surgery is only a single room in someone else's house—there is simply not the space in which to put the 20 or more separate sterile syringes, each ready for use.

Dr. MERVYN GOODMAN (Liverpool, 18) writes: The simplest and most efficient expeller for calf-lymph vaccine is, to my mind, the teat of a baby's feeding-bottle. The ends of the lymph tube are broken off and inserted in the small hole. The teat is held between the index and middle fingers with the thumb over the large aperture, which is made to fit on the bottle. Gentle pressure by the thumb readily expels the lymph. The cost is a matter of pence, and the method has given me no trouble in the past eight years.

"Imferon" and Cancer

Dr. R. G. WOODWARDS (Birmingham, 25) writes: Two questions occur to me on this subject. (1) I understand massive doses of iron have been administered to rabbits and guinea-pigs with no ill effects. This fact seems to have escaped notice. (2) Should we not order the speedy withdrawal of stilboestrol, glucose, fructose, arachis oil, etc., all of which have produced tumours under similar extreme experimental conditions?

Health Tax on Tobacco

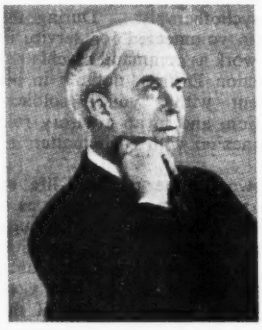
Dr. GILBERT R. SMITH (Birmingham, 20) writes: Since the United Nations' World Health Organization has at last seen fit to release a formally expressed opinion that smoking is a major cause of lung cancer; and since there can be no doubt that smoking is a major factor in the prevalence of upper respiratory infection in all sections of the community; and since, as a result of rising costs and estimates, it is inevitable that the amount of the personal contribution must increase, is it unreasonable to suggest that there should be a "health tax" enforced on the sale of cigarettes and tobacco?

Obituary

Sir ROBERT McCARRISON, C.I.E., M.D., D.Sc. LL.D., F.R.C.P.

Major-General Sir Robert McCarrison, formerly of the Indian Medical Service and first director of the Nutrition Research Laboratories, Coonoor, Southern India, died in his sleep on May 18, aged 82. His work had a relation first of all to India, to which the best years of his life were given, but extended far beyond it, and his studies, particularly on goitre, cretinism, and deficiency diseases, were outstanding contributions to medicine in general.

Robert McCarrison was born at Portadown, Co. Armagh, on March 15, 1878. He studied medicine at Queen's College, Belfast, and in Dublin, graduating M.B., B.Ch. (with first-class honours) in 1900. He proceeded M.D. in 1909, taking the M.R.C.P. in the same year. He was elected F.R.C.P. in 1914, and obtained the degree of D.Sc. (Belfast) in 1915.



Entering the Indian Medical Service not long after qualification, he soon became known as a research worker of the first order, and in 1911 he received the Kaisar-i-Hind gold medal in the first class for public medical services.

The war of 1914 interrupted his research work, and he went on active service, working in a large Indian general hospital in Egypt. While there his health broke down, and he was sent to England, where he was placed in charge of the Malaria Investigation Hospital. In 1918 he was gazetted brevet lieutenant-colonel for distinguished service in the field.

Returning to India in that year, he began work in the Pasteur Institute, Coonoor, and remained there until his retirement in 1935, when he came to England, settling at Oxford. An Indian scientific journal said that "his retirement has deprived this country of a devoted scientist whose selfless labours have won for him not only public recognition but the personal esteem of all who have come into contact with him."

Many honours came to him. He was appointed C.I.E. in 1923 and was knighted ten years later. In 1922 he was appointed one of the twenty Honorary Fellows of the College of Physicians of Philadelphia. In 1918 he received the Hon. LL.D. of his alma mater, Queen's University, Belfast. From 1928 to 1935 he was Honorary Physician to the King. In 1934 the governing body of the Arnold Flinker and Julius Wagner-Jauregg Foundation of Vienna awarded him the Foundation's prize for his researches into the aetiology of goitre, on which he had presented a report at the second International Congress on Goitre held at Berne the previous summer. This prize had never before been awarded to a foreigner, and the statutes had to be altered accordingly. Other prizes he received were the Arnott memorial gold medal of the Irish Medical Schools and Graduates Association in 1922 and the silver medal of the Royal Society of Arts in 1925. His Cantor lectures to the Royal Society of Arts were published in book form with the title *Nutrition and Health*.

In 1918 the British Medical Association awarded him the Stewart Prize for valuable researches in reference to the origin, spread, and prevention of epidemic disease; other Stewart prize-men have been Sir Patrick Manson, Sir David Bruce, and Sir Almroth Wright. McCarrison joined the British Medical Association in 1904. He was vice-president of the Section of Nutrition at the Oxford Meeting in 1936, and president of the same Section at Belfast in 1937. He was chairman of the Oxford Division for several years during the second world war, and served as a group officer in the Emergency Medical Service. After the war, from 1945 to 1955, he was director of postgraduate medical education at Oxford.

McCarrison was the possessor of a distinguished and commanding presence and he had no slight oratorical gifts. His audiences felt the infection of his own enthusiasm although the subject might be completely new to them. He brought to his researches not only a critical mind and a severe self-discipline but also imagination and a philosophic outlook. His love for India was manifest, and India rewarded him with an affection which she has given to few Europeans.

He married in 1906 Helen Stella Johnston, who survives him.

Dr. W. R. AYKROYD writes: The Indian Medical Service gave Sir Robert McCarrison opportunities for a remarkable career mainly devoted to medical research and in particular to the pioneer research on nutrition which earned him world-wide renown. On arrival in India he was immediately posted as regimental medical officer to Chitral in the Hindu Kush. Here he did his first research, on a then obscure disease which he called the "Three-day Fever of Chitral," surmising, correctly, that it was transmitted by the sandfly.

In the first decade of the century a young I.M.S. officer interested in research naturally turned his attention to infectious disease: the modern science of nutrition had yet to be born. McCarrison showed striking originality at an early stage in his career in turning his mind to the relation between nutrition and health. During his service in Chitral, Gilgit, and elsewhere on the frontiers of Northern India, he was struck by the fine physique and powers of endurance of the local people, and conceived the idea that these characteristics might be due largely to their diet—a diet of wholemeal flour, milk products, vegetables, fruits, with a little meat on rare occasions. This concept was the basis of much of his later work.

The good health and physique of the Himalayan peoples were marred in some areas by goitre and cretinism, a problem to which McCarrison next turned his attention. The results of his investigations were described in various publications, including the Milroy lectures—on the subject of the aetiology of endemic goitre—which he gave before the Royal College of Physicians in 1913, and a book entitled *The Thyroid Gland in Health and Disease*. In his research on goitre, which he continued until 1935, McCarrison adopted the approach which proved fruitful in his broader studies on diet and disease—that is, a combination of field observations and investigations on laboratory animals.

His long series of publications on goitre are difficult to summarize. He did not question the importance of iodine deficiency in causation, or the effect of iodine as an anti-goitrogenic agent, but at the same time insisted that a significant part was played by other factors, including sanitary conditions, goitrogenic substances in certain foods, and the general composition of the diet. His work on goitre brought him world-wide recognition. He received in 1914 the Prix Amussat of the Academy of Medicine in Paris and was invited to lecture by numerous medical and scientific societies and organizations in England and America.

His major work, *Studies in Deficiency Disease*, published in 1921, can still be read with interest and profit; it has the pungency and freshness of the earlier editions of McCollum's *The Newer Knowledge of Nutrition*. Its publication was preceded by the establishment in 1918 of a nutrition research unit under McCarrison's direction in the Pasteur Institute in Coonoor in South India. Originally composed of McCarrison and a single unqualified assistant, the research unit grew step by step, surviving interruptions and even an "axeing" by the Government of India in 1923, into the Nutrition Research

Laboratories of the Indian Research Fund Association (now the Indian Council of Medical Research). The laboratories, transferred to Hyderabad in 1959, are generally regarded as being the leading institution for nutrition research in Asia. The staff now includes 30 professional research workers.

From 1919 to 1935 McCarrison built up the Laboratories, carried out a wide variety of investigations, and, in his own words, put nutrition "on the map" in India. Much of the research was simple in conception. Rats were fed on "good" and "bad" diets, resembling diets eaten by human beings in India and elsewhere. On the good diets they thrived; on the bad, they failed to grow, suffered from all manner of disease, and died prematurely. From these and other experiments and field observations, a picture of the problem of nutrition in India emerged, and medical and public-health authorities, administrators, and the educated public began to realize its importance. McCarrison's laboratories did much to define the problem, still as far from solution as when they were first established. To say that many of his conclusions now appear obvious is to pay him a high compliment. They were far from obvious forty years ago.

Throughout his service McCarrison followed his own individual bent, not always with enthusiastic support from his administrative chiefs. He was sometimes described by I.M.S. colleagues as "a lone hand." In the Lloyd Roberts Lecture, delivered in 1937 to the Medical Society in London, he gave an account of his work in India under the appropriate title of "Adventures in Research." Lacking conventional scientific training, he nevertheless had a remarkable aptitude for making original observations and designing experiments, and a flair for seeing the wood rather than the trees.

Many of his contributions to nutritional science are solid and enduring, and in India he is remembered both as a pioneer discoverer and as the founder of the Nutrition Research Laboratories. He was aware of the social implications of his work and of the need for educating people in better habits of diet. He was fond of telling the missionaries who often visited the Coonoor Laboratories that he was also a missionary and had found a suitable text for his sermons. This was: "Hearken diligently unto me and eat ye that which is good" (*Isaiah* lv. 2). He himself followed his own dietary tenets, a tendency rare among nutrition workers. For example, he regarded refined white flour as a defective food and for many years breakfasted on whole-wheat chappaties. His distinguished appearance, of which he was agreeably aware, was a valuable asset; the abundant wavy hair, clear complexion, and Irish accent made an attractive ensemble.

When the Royal Commission on Agriculture in India visited Coonoor in 1926 one of its members, the Rajah of Parlakimedi, was so impressed by McCarrison and his exposition that he handed him a lakh of rupees (£7,000) across the table, a donation subsequently used to create two Parlakimedi research fellowships, the first fellowships in India supported by a private gift. As a formal lecturer, McCarrison was often truly eloquent, evoking an enthusiastic response from his audiences. In his relations with young colleagues and Indian subordinates he was kind and courteous, a quality which he displayed to advantage when, after his retirement from India, he served from 1945 to 1955 as director of postgraduate medical education at Oxford.

McCarrison's contributions to science were described in detail in the volume *The Work of Sir Robert McCarrison* (edited by H. M. Sinclair) published in 1953 on the occasion of his 75th birthday. E. V. McCollum, another pioneer nutrition research worker, wrote of him in that volume as follows:

> "Sir Robert possesses in enviable measure qualities which are admirable in the eyes of his many friends and admirers. Intellectual honesty, enthusiasm, curiosity, studious attention to interpreting his observations in the full light of the work of others, courage of conviction in unusual measure in defending his considered conclusions are characteristic of him. He possesses not only knowledge but wisdom."

L. F. BROWNE, M.D.

Dr. Leonard Browne, honorary consultant psychiatrist to the Tavistock Clinic, died at his home in London on May 15. Aged 72, he had been in failing health for the past two years.

Leonard Foster Browne was born on May 22, 1887. From Sedbergh he went on to the University of Durham to study medicine, graduating M.B., B.S. in 1909. After holding the post of senior house-physician at the Royal Victoria Infirmary, Newcastle-upon-Tyne, he worked for a time at the Newcastle Dispensary before proceeding M.D. (with gold medal) in 1913. A staunch Anglican, he went out to the Church Missionary Society's hospital at Cairo as assistant surgeon in 1912, but on the outbreak of the first world war he joined the R.A.M.C. and saw service in France and Flanders. One of the founders of Toc H, he continued to be greatly interested in that movement to the end of his life. He was ordained a deacon in 1923.

After the war he joined the staff of the Tavistock Square Clinic (now the Tavistock Clinic) for Functional Nervous Disorders, and it was not long before he built up a successful reputation as a consultant psychotherapist. During the second world war Browne again volunteered for service in the R.A.M.C. and did valuable work as command psychiatrist of Eastern Command and London District, notably in his supervision of the experiment with "young soldiers' battalions," in personnel selection, and in an advisory role to commanding officers in connexion with such matters as morale and delinquency.

Browne was also well known in the political life of London. An old Fabian, he served for many years as a member and later as an alderman of the St. Pancras Borough Council. From 1946 to 1949 he represented North Kensington on the London County Council, and from 1949 until his death he was a county alderman. He was also vice-chairman of the council in 1957–8. As chairman of the special education subcommittee of the L.C.C. he was able to render informed help to the cause of child guidance and of handicapped children in London. He stood unsuccessfully for Parliament as a Labour candidate for Penrith and Cockermouth at the General Election in 1945.

Dr. Browne married in 1923 Violet, daughter of the Rev. Richard Bott. She survives him with their three children, two of them doctors.

Dr. H. V. DICKS writes: After the first world war, Browne was one of the small group of doctors round the late Dr. Hugh Crichton-Miller (whose obituary was published in the issue of the *Journal* dated January 10, 1959, p. 116), who had learnt the value of the "New Psychology," made obvious by the successes in the cure of shell-shocked soldiers. He was thus one of the earliest staff members of the Tavistock Clinic, and underwent a didactic analysis. It was as a well-known consultant psychotherapist that Browne was to spend the remainder of his successful and fruitful maturity. A valued senior staff member and lecturer at the Tavistock Clinic in the inter-war years, he was at his best as a cool, wise head in committee and in policy-making, enlivening the proceedings with his quiet humour and imperturbable common sense. With his background of Christian ethics and experience he was in demand for many collaborative and educational enterprises between psychiatry and the clergy.

After the second world war, Browne, with his progressive and adaptable mind, was in full sympathy with the transformations in Tavistock-Clinic policy which evolved the Institute of Human Relations. He rendered inestimable service to this young and novel institution by his years of service on its governing council, of which he for some years was vice-chairman. He was too old to resume his clinical appointment under the National Health Service Act, and the Tavistock Clinic honoured him by appointing him an honorary consultant psychiatrist.

In other ways, too, Browne actively helped the broad cause of mental health. He was an enthusiastic supporter

of the London Mental Health Congress in 1948, and he lectured most successfully for the World Federation for Mental Health in many cities of the U.S.A. on his way to a later congress in Mexico. The other half of Browne's life—his dedicated political service—was of a piece with his humane values as a physician and social psychiatrist.

Leonard was to his many friends and colleagues a constant source of sage and good counsel, accessible and unpretentious. He befriended many refugees from Central Europe. He loved his cottage on the shore of Derwentwater, and was a keen walker and a man of the Fells. He published little. He has left behind him only two major contributions—"Psychotherapy in the Treatment of Tuberculosis," showing an early appreciation of the psychosomatic viewpoint in medicine, and a joint paper with J. A. Hadfield (whose views he largely shared) on "The Psychology of Spiritual Healing." Leonard Browne was a noble example of a Christian Socialist, and a lovable, upright man of fearless honesty, with the added grace of his clinical and psychiatric training and his capacity for kindly laughter at himself and the world at large. All his colleagues will wish to extend to his widow and children their sense of shared loss.

W. A. L. DUNLOP, M.B., B.Ch.

Dr. W. A. L. Dunlop, who had practised in Hendon for many years, died on April 23 aged 69.

William Anketell Leeper Dunlop was born on November 23, 1890, and studied medicine at Queen's College, Galway, and Queen's University, Belfast, where he graduated M.B., B.Ch. with honours, being awarded a gold medal and a scholarship. After holding the post of medical officer at the Royal Infirmary, Sunderland, he practised for a short time in a Welsh mining village, and then joined the R.A.M.C., serving in the firing-line on the Western Front as medical officer to the Rifle Brigade. Later he became an Army medical officer of health at Baku. On demobilization he was appointed house-surgeon to the Queen's Hospital for Children in London, and it was there he met his wife, Dr. Doris Howard. Joining Dr. Frank Andrew at Hendon, he remained in general practice there for thirty-five years. During the second world war he carried on his own and his partners' practice in addition to acting as medical officer to the local mobile surgical unit.

Dr. Dunlop leaves a widow, a son, Dr. Ivor Dunlop, and a daughter.

Mr. NORMAN COLLINS writes: To the end of his days Dr. Dunlop remained the typical Ulsterman—bluff, zealous, independent, humorous, and kindly. Every one of his patients will have some private individual memory of his unfailing sense of duty. My own family remembers best one night when the fog was so thick that it was impossible to use a car, and Bill Dunlop, as even the children came to call him, walked from Hendon to Hampstead at 12 o'clock at night to see my eldest daughter who had fallen suddenly ill.

I remember, too, one night during the blitz when Bill Dunlop had allowed himself his first free evening for weeks. We stood together beside the White Stone Pond on Hampstead Heath and watched London, under a salmon-coloured sky lit up by the flames beneath, burning itself to what looked like all but total destruction. The spectacle was majestic and terrible. After a particularly vivid burst of flame somewhere over Dockland, Dr. Dunlop nudged my arm. He had decided that, even though it was not his night on duty, every doctor in London would be needed, and he drove back to another sleepless night of National Service. The surgical unit to which he was medical officer during the second world war was constantly on the move, always arriving at the "incidents," as they were so strangely called, while the bombs were falling all around. It was a tired but still smiling Bill Dunlop that I knew in those days. Even so, after the war the indefatigable Dr. Dunlop continued his connexion with the armed Forces by serving on the recruiting medical boards. At his cremation on April 25 the little chapel was crowded with friends and patients—and to be his patient was also to be his friend. As a memorial to him in the part of London which he loved so well his friends are collecting for a garden seat to be erected in one of Hendon's parks.

E. J. ROMBEJKO, M.D.

Dr. E. J. Rombejko, a medical officer in the Overseas Civil Service, died on February 28. He was 45 years of age.

Edward Joseph Rombejko studied medicine at the University of Warsaw, graduating in 1938. At the outbreak of the second world war he joined the Polish Army. After the fall of Poland he was a prisoner-of-war in Germany until 1944, when he was released by the Allied Forces. He then served in the Navy, taking part in the Russian convoys, until his demobilization in 1946. He resumed his medical studies as a postgraduate at Stobhill Hospital, Glasgow, and then entered general practice as an assistant in the Clydebank area. In 1951 he became a British subject, and in 1953 he joined the Overseas Civil Service. He was posted to St. Helena for three years. In 1956 he was transferred to Sierra Leone and worked at Bo, Kenema, and Lungi. Last January he was posted upcountry to Makeni, where, as the only doctor, he worked under great difficulties for six weeks, when he contracted a fever himself. He remained on duty for 10 days until assistance arrived, when he was flown to Freetown, where he died in hospital.

Dr. T. N. FRASER writes: Edward Rombejko was dedicated to his work and to the service of humanity. This devotion was above race, religion, and politics. His quiet charm and courtesy endeared him to his patients in Clydebank, St. Helena, and Sierra Leone, as well as to his friends. He gave of his best to the Africans, and they loved him dearly. Four hundred Africans attended his funeral, and prayers were said in churches of every creed.

Our sympathy goes out to his widow, Sophie, who nursed him alone through his tragic illness.

D. R. K. R. writes: The untimely death of Edward Rombejko is a sad loss to his many friends in West Africa, France, and England, and not least in Scotland, where he found his spiritual home. War, exile, and an early death robbed him of the surgical career that otherwise he might have sought; certainly, when he came to us for surgical experience, he proved an apt and enthusiastic pupil, and in a remarkably short space of time acquired a high degree of surgical competence. Edward was a fine man, gay and charming, courteous and considerate, and his death is a grievous blow to the service and the profession which he graced and served so well. We can only deplore the manner of his going and offer his widow our heartfelt sympathy.

E. R. THOMAS, L.R.C.P.&S.Ed.

Dr. E. R. Thomas, formerly in practice at Beaumaris and later at Rhyl, died on April 5 at his home in Old Colwyn at the age of 88.

Edwin Robert Thomas was born on October 26, 1871, at Dowlais, Glamorgan, and was educated at Bangor. After qualifying at Edinburgh in 1900, he settled in Beaumaris, where he practised for about 30 years. During this period he, like many of his generation working in country districts, had to do a variety of clinical work which would now be undertaken in hospital. This brought out his resourcefulness, and he acquired a reputation as a skilful obstetrician over a wide area. He held many appointments, including that of medical officer of health. A quiet, conscientious doctor, he was a man of deep religious convictions.

In 1920 he married Miss Phoebe Jones, matron of the Caernarvonshire and Anglesey Hospital, Bangor, and it proved to be a most happy partnership. In 1927 he moved to Rhyl and retired in 1940 to Colwyn Bay. During his last illness he was most considerate and grateful to his

attendants, and the sympathy of his medical colleagues and his host of friends goes to his widow, who, though in poor health for some years, attended to him without sparing herself.—J. P. E.

R. MACKINNON, M.B., Ch.B.

Dr. R. Mackinnon, who practised until recently in Murton, County Durham, died at Tor Na Dee Hospital, Aberdeen, on April 6 at the age of 54.

Roderick Mackinnon was born at Portree, Isle of Skye. He studied medicine at the University of Glasgow, graduating M.B., Ch.B. in 1929. After a period of assistantships on Tyneside and in County Durham he settled in practice at Murton, County Durham, and remained there until ill-health necessitated his retirement about eighteen months ago.

W. A. H. and A. A. McI. N. write: It was with deep regret that we heard of the death of Dr. Roderick Mackinnon. He was in every sense of the term a "good doctor," efficient, up-to-date, conscientious, and kindly. He hated and detested all sham and make-believe, and on occasion was forthright and outspoken and had no patience with the malingerer. Hence it was that his practice was excellently attended to, and he kept records which were an example to all. For over 25 years he was a devoted medical officer to Leeholme Hospital at Easington, at first under the Durham county public assistance committee and later the Sunderland hospital management committee, by whom his services were highly appreciated. During this period he was also anaesthetist and gave much of his time and study to this branch of his work, for which he showed a special interest and aptitude. In later years the anaesthetic service of the Thorpe Maternity Hospital was included in his work, and there is no doubt that he overworked.

He loved the country, fishing, and the study of ornithology, of which he had extensive knowledge. On his retirement his patients, friends, and colleagues presented him with a worthy testimonial, and his loss is deeply felt. He retired to his native Skye in the hope that his health would recover, but this was not to be, and for the last six months he was in the hospital where he died. He was laid to rest in his beautiful isle, near the sea and in sight of his beloved Cuillins. He leaves a widow, to whom deep sympathy is extended.

Z. M. H. R. writes: The co-operation and friendship between Mr. W. A. Hewitson and Dr. Mackinnon was very wonderful. Dr. Mackinnon was devoted to his chief. Apart from work they had many interests in common. He never failed to rise to the occasion at Leeholme Hospital, where there was no resident and where Mr. Hewitson did major surgery. He turned out at all hours of the day and night to give anaesthetics, blood transfusions, and to attend to emergencies. He had very high ideals which he put into practice. His wife and he were a very devoted couple, and she was a very great help to him in the business side of his practice. My only regret is that he did not pass away looking out from the window of his beautiful new bungalow across Portree Bay to his beloved Cuillins.

NOEL E. WATERFIELD, O.B.E., M.B., B.S., F.R.C.S.

The obituary of Dr. Noel E. Waterfield was published in the *Journal* of May 7 (p. 1434).

Mr. B. BRENDAN HICKEY writes from Swansea: I had the privilege of meeting Dr. Waterfield in 1954 when he visited the Sudan and took a keen interest in the surgical work there. He came round my beds and spoke to each patient in perfect Arabic. He was one of a now diminishing band of pioneers who brought civilization to what was one of the most primitive countries in the world. They gave their services cheerfully, and under conditions which few would now tolerate. The journey from Khartum to Omdurman (which now takes 20 minutes by road) had to be done by boat, taking up to two hours under a blazing sun, and this was only an incident in a day's work. Financial reward meant little. The Waterfield prize in surgery in the Kitchener School of Medicine was given by him after an unexpected salary rise which he did not feel justified in accepting, and was passed on to the Sudanese.

D. A. DONALD, *M.C.*, M.B., Ch.B.

Dr. D. A. Donald, who practised for over 40 years in North Berwick, died at Edinburgh on April 19, after a short illness.

Douglas Allan Donald was born on September 29, 1888, the son of the parish minister of Moulin and Pitlochry. From Sedbergh School he went on to the University of Edinburgh to study medicine, graduating M.B., Ch.B. in 1912. After working as house-surgeon at the North Riding Infirmary, Middlesbrough, and as clinical assistant in the medical wards of the Edinburgh Royal Infirmary, he joined the R.A.M.C. in 1915. He served in Gallipoli and in France, where he gained the Military Cross, and from each campaign was invalided home seriously ill.

In 1919 he bought Dr. Frank Crombie's practice in North Berwick, where he worked until his recent retirement. He was able to enjoy only five days of this when his final illness began. His 40 years of hard and devoted work earned him the sincere affection and gratitude of his patients, and a sense of tragic loss has hung over the community at the news of his illness and death.

A keen sportsman, Dr. Donald was reckoned one of the best guns in the county of East Lothian and was a very keen and knowledgeable angler. Although never a good golfer like his daughter Jean, he always played with enthusiasm and was honoured by being appointed captain of the Tantallon Golf Club during its centenary year, and he was captain-elect of the New Club, North Berwick, at the time of his death.

His success as a general practitioner was due in no small part to his wife, and we offer to her and her three married daughters our most sincere sympathy.—J. MacD

Medico-Legal

SUBPOENA BY PROFESSIONAL DISCIPLINARY BODIES: SIMONDS COMMITTEE REPORT

[FROM OUR LEGAL CORRESPONDENT]

One of the questions arising out of the case of Dr. Kenneth Merrall Fox before the Disciplinary Committee of the G.M.C. last December (*Supplement*, December 5, p. 182) concerned the power of professional disciplinary bodies to compel the production of evidence by subpoena, and in particular to compel such production by the police. On January 5 a departmental committee under the chairmanship of Lord Simonds was set up to consider the matter. The committee's terms of reference were "to consider to what extent and subject to what conditions subpoenas (or in Scotland citations) should be issuable to secure the attendance of witnesses and the production of documents before disciplinary tribunals; and in particular to consider whether subpœnas should be issuable to secure the production before such tribunals of evidence obtained by police officers in the course of criminal investigations; and to make recommendations." The Simonds Committee have now reported.[1]

"All the Relevant Evidence"

The Committee base their report on the fundamental principle that, in the administration of justice, it is essential

[1] *Report of the Departmental Committee on Powers of Subpoena of Disciplinary Tribunals*, 1960, Cmnd. 1033. H.M.S.O., London.

that the court or tribunal should have before it all the relevant evidence that is available. This is particularly important in the case of professional tribunals, where the penalties imposed are so grave, and it is essential that in proceedings before such tribunals prosecutor and accused alike should have power to enforce the attendance of witnesses. The Committee cite memoranda of the G.M.C. and General Dental Council in practical support of this theoretical principle. Both those bodies, and certain other tribunals, have the statutory powers to secure the issue of subpoenas which are effective throughout the United Kingdom. The Committee recommend that those statutory disciplinary tribunals which now lack the power to secure the issue of subpoenas, and any such bodies as may be created in future, should have such power conferred upon them. This recommendation applies equally to Scottish tribunals, which should have the power to issue citations. The committee consider that no check should be imposed on the issue of such subpoenas beyond the normal remedy of moving the High Court to set aside the writ of subpoena.

"Citizens in Uniform"

The Committee recommend that the police should stand in a position no different from that of a private citizen as regards the writ of subpoena. The policeman is "but 'a citizen in uniform,' and it might be thought paradoxical that just because he has a special opportunity of acquiring information he should therefore be allowed or required not to impart it." Of course, the public interest sometimes overrides the demand for justice for the individual, and in such cases the witness, when he is before the tribunal, may claim to be privileged from answering some or all of the questions put to him (in some rare cases the Crown privilege will be so apparent on the face of the subpoena that the writ ought not to issue). The extent of Crown privilege was not within the terms of reference of the Committee, but the Committee delivered an *obiter dictum* (of the utmost weight, coming as it does from three distinguished Law Lords) covering the facts of Dr. Fox's case:

> "There is . . . a wide field where no plea of Crown privilege is available. A police officer in the course of what may fairly be called a 'criminal investigation' hears or sees something which may be of material importance to an inquiry before a disciplinary tribunal. He may, for instance, actually witness, and perhaps be the only witness of, conduct which, though falling short of a crime, is disgraceful in the professional sense: he may be invited or allowed to 'listen in' to a telephone conversation and so be able to corroborate the evidence of the listener about something said by the speaker. In such cases we see no reason why he should not be required to give evidence on subpoena and it is clear that no plea of privilege would avail. It would in our opinion be intolerable if the course of justice was defeated by the withholding of evidence in such cases."

This statement, of course, does not apply to secret telephone "tapping," but only to invitations to "listen in" at the listener's end of the line.

The possibility of a plea of privilege and questions of admissibility of evidence generally are clearly likely to give difficulty to lay tribunals, and the Committee therefore recommend that any disciplinary tribunal should have available to it legal advice for assistance in the general conduct of its proceedings and for guidance in ruling on the admissibility of evidence and on claims of privilege. (The G.M.C. has the assistance of a Legal Assessor—see *British Medical Journal*, December 12, p. 1316.)

Professions Supplementary to Medicine Bill

The report of the Simonds Committee has considerable bearing on the Professions Supplementary to Medicine Bill, which, as originally drafted, was designed to give powers of securing the issue of the subpoena to the disciplinary tribunals to be set up for the auxiliary medical professions: this provision, however, was removed from the Bill at the Commons committee stage, leaving available only the less effective Common Law powers to secure the issue of the writ. The Simonds Committee express a firm distaste for giving disciplinary powers to a professional body without the power to exercise the jurisdiction fairly and properly. Such jurisdiction should either be completely withheld, or should be given with full powers, the safeguard being that each tribunal should be fitted and equipped to deal with matters of evidence in accordance with established legal principles.

CORONERS' CASES

Asphyxia During Caesarean

Asphyxia due to a closed valve on an anaesthetic apparatus was described at Edinburgh Sheriff Court on March 24, where an inquiry was held into a woman's death at the Simpson Memorial Maternity Pavilion. Mrs. Mary Wales, aged 34, was undergoing a caesarean operation on January 28, when, soon after its start, she was noticed to be cyanosed. The anaesthetist at once checked the machine and observed that the flow meter was registering that oxygen was flowing. In fact a valve, which was later found in the "off" position, was preventing the oxygen from reaching the patient and it was escaping through the outlet valve. This registered a flow on the indicator. Changing the position of the intratracheal tube made no difference to the patient's condition, and soon afterwards her heart stopped beating. Mr. Alastair Maxwell, who was performing the operation, opened the chest and massaged the heart, which started to beat after some minutes. At this point he observed that the valve on the closed-circuit apparatus, situated at the junction, was in the closed position. Mrs. Wales died the next day.

At the inquiry Mr. Maxwell agreed that death could have been due to either anoxia or amniotic embolism, or both together. Sheriff Sir James Gilchrist, Q.C., instructed the jury that there was insufficient evidence to warrant their making any special finding of fault, and asked that a formal verdict be returned. They returned a verdict of accidental death (*Glasgow Herald*, March 25).

Medical Notes in Parliament

FUNDS FOR MALARIA ERADICATION

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Lord AMULREE found a number of supporters for a suggestion he made on May 18 that the Government should make a special contribution to the Malaria Eradication Special Account which would be sponsored by the World Health Organization. The Government's attitude, as stated by Lord ST. OSWALD, a Lord-in-Waiting, was that they already contributed substantially to the regular budget of the World Health Organization and other international funds which devoted large sums to antimalaria work; and also to the cost of such work in United Kingdom oversea territories. They did not feel able therefore to make an additional special contribution to this account.

Lord AMULREE urged that the Government should think again, pointing out that the Director of W.H.O. had said that it should be possible for malaria to be eradicated from the world by 1970 if the fund was fully subscribed to. The Governments of the United States and the Soviet Union were making large contributions to this fund. The malarial mosquito was becoming more and more resistant to being killed by D.D.T. and similar substances. Although the Government gave considerable sums to W.H.O., could they not make an exception in this case, in view of the urgency? Lord ST. OSWALD said it was the Government's view that voluntary extra-budgetary funds were not a sound way of financing continuing programmes of international organizations which had a regular budget. All activities undertaken by W.H.O. should form part of a co-ordinated programme within a regular budget drawn up in accordance with predetermined priorities. He repeated that United Kingdom contributions to the main account were substantial, coming third after the United States and Russia. The Russian contribution to the special account was not very great.

Government Unyielding

The Earl of LUCAN emphasized that this was something additional to the ordinary work of the W.H.O., and that the total expenditure for 1959 from contributions was 45 million dollars. Lord ST. OSWALD agreed that the United States had contributed generously to this special account. But in the eradication of malaria the United Kingdom record was high in its own territories. In Singapore and Malaya it had been completely successful; in Sarawak and Zanzibar and many parts of the West Indies eradication was in sight, and in North Borneo and Trinidad programmes had begun.

Lord TAYLOR pointed out that the malaria mosquito did not respect territorial boundaries, and it was necessary to assist eradication in neighbouring territories. Lord SHEPHERD said it would be better to spend more money now and achieve eradication rather than to have continual expenditure without eradication. Lord ST. OSWALD said the Government's view was that this was not best done by a Special Account, entered upon without any assurance that it would be fully subscribed, and possibly producing a programme which could not be completed. Lord REA and Viscount ALEXANDER OF HILLSBOROUGH added their support, but Lord ST. OSWALD was not to be moved from the contention that the method proposed by Lord Amulree was not the most likely to achieve the complete result the Government were aiming at.

QUESTIONS IN THE COMMONS

66 Murder Charges Reduced

The HOME SECRETARY stated in answer to Dr. DONALD JOHNSON (Carlisle, Con.) on May 19 that since the Homicide Act was passed on March 21, 1957, there had been 66 persons who were originally charged with murder but were found guilty of manslaughter by reason of diminished responsibility under Section 2 of the Act. Dr. JOHNSON: In view of this really considerable number of people, will the Home Secretary watch the operation of the section carefully? It seems that in some instances, such as the recent Birmingham murder, the more horrible the crime the lighter is the penalty inflicted through the operation of that section. Mr. R. A. BUTLER: Yes, provided it is realized that the law is now being interpreted as passed by Parliament, and the only way of altering it would be fresh legislation. I will certainly watch the situation, but I would rather not give any undertaking about fresh legislation at the present time.

Psychiatric Prison

Mr. KENNETH ROBINSON (St. Pancras North, Lab.) asked the Home Secretary to what extent the plans for Grendon Underwood penal establishment had been modified since the original conception; when construction was expected to start; and if he would make a statement on the proposed function of this establishment. Mr. BUTLER said the concept of a psychiatric prison originated a number of years ago and had been developed in the light of modern penal methods. Construction had already begun. The prison would provide psychiatric treatment for prisoners who, though not insane or mentally deficient, were recommended for this by prison medical officers following observation.

Mr. ROBINSON asked if that meant that all prisoners in this establishment would be drafted from other prisons. There was now some confusion, since the passing of the Mental Health Act, about what was the appropriate form of treatment for a criminal psychopath as between a penal and a hospital setting. Mr. BUTLER replied that there was this difficulty. People would not be drafted direct to this prison, and would go there on the recommendation of the prison medical officer concerned. They must work on the difficult and delicate point Mr. Robinson had raised in the light of experience gained in the early days of this prison.

Cremation Certificate Charges

Mr. GEORGE THOMAS (Cardiff, West, Lab.) stated in a question to the Home Secretary that doctors in some Health Service hospitals were charging four guineas for signing a cremation certificate, in spite of the B.M.A. recommendation that two guineas was an adequate fee; and asked if the Home Secretary would exercise his statutory powers to regulate the fees that doctors might charge. Mr. D. VOSPER Under Secretary, told him that the Home Office was reviewing the cremation regulations, including the question of prescribing fees for certificates. Mr. THOMAS said there was a great deal of social injustice involved when hospitals within the same city charged different fees for the production of these certificates. The sooner action was taken the better. Mr. VOSPER replied that there was a voluntary scheme in effect through the co-operation of the B.M.A., and generally it had worked well. The question now arose whether some compulsory condition should be imposed. If Mr. Thomas would send him particulars of cases where a fee of more than two guineas was charged he would look into them.

Universities and Colleges

UNIVERSITY OF OXFORD

Dr. Edith Bülbring, F.R.S., has been appointed Reader in Pharmacology from October 1, 1960, to September 30, 1967.

Dr. D. G. Jamison, Lecturer in Physiology in Corpus Christi College, has been elected to a senior research fellowship at the college, with effect from October 1, 1960.

Dr. K. E. Cooper has been elected into a Lectureship in Physiology at St. Peter's Hall with effect from October 1, 1960.

UNIVERSITY OF CAMBRIDGE

In Congregation on April 30 the following degrees were conferred:

M.D.—J. E. Forster, D. R. Bowsher, C. D. Evans.
M.CHIR.—*W. G. Williams.
M.B., B.CHIR.—*D. A. Wright.
M.B.—*M. J. Orrell, R. A. Lewin, D. F. Ll. Watkin, P. Snell, A. Harley, P. J. N. Howorth.

*By proxy.

Dr. J. T. Fitzsimons has been approved for the degree of Ph.D.

In Congregation on May 14 the degree of M.B. was conferred on C. L. C. Arnold.

UNIVERSITY OF ST. ANDREWS

Dr. J. T. Hemingway has been appointed to a Lectureship in Physiology in Queen's College, Dundee, as from October 1, 1960.

UNIVERSITY OF LONDON

The following have been appointed or renominated as representatives of the University on the governing bodies of the colleges indicated in parentheses: Dr. Katharine G. Lloyd-Williams (Bedford College); Professor Esther M. Killick (Queen Elizabeth College).

Professor Wilson Smith, F.R.S., has resigned from the chair of bacteriology at University College Hospital Medical School, as from September 30, 1960.

The following candidates at the Institute of Psychiatry have been approved at the examinations indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN PSYCHOLOGICAL MEDICINE.—M. F. Dixon, W. R. Little. *Part I only:* J. J. Cockburn, Mary K. Coghlan, J. G. Edwards, Eva A. Frommer, D. R. Gander, M. G. Gelder, R. U. Gillan, B. J. Gurland, A. D. Isaacs, C. McCance, W. O. McCormick, Lorna I. M. Maclay, A. L. Parker, V. Satkunanayagam, E. B. O. Smith, C. M. Tonks, J. E. S. Varley.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on May 12, with Sir James Paterson Ross, Bt., President, in the chair, Dr. Frankis T. Evans, Surgeon Captain J. L. S. Coulter, Dr. E. F. Scowen, and Professor E. C. Amoroso were admitted to the Fellowship after election.

The Jacksonian Prize was presented to Mr. Geoffrey Slaney, F.R.C.S.

The Lady Cade Medal was awarded to Group Captain Ralph Coburn Jackson, M.R.C.S., L.R.C.P.

Begley Prizes were awarded to J. Barrett, of St. Thomas's Hospital Medical School, R. Eldon Robinson, of St. Mary's Hospital Medical School, and G. A. Hunter, of University College Hospital Medical School.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

At a meeting of the President and Fellows held on May 6, Andrew H. Davidson, M.D., F.R.C.P.I., F.R.C.O.G., was re-elected King's Professor of Midwifery in the School of Physic, Ireland.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The following candidates have been awarded the Diploma in Obstetrics:

Margaret E. Abel, Shirley A. P. Abell, Eleanor M. Adams, J. F. R. Adams, A. Addison, Delia M. Aitken, Razia Akbani, J. Armstrong, J. R. Ashwood, D. Atkinson, F. G. Atkinson, Safiya Azimuddin, J. K. Baird, R. Baird, Ramala Bakaya, P. J. Ball, R. M. Barnes, Maureen E. Barr, D. G. Barrowcliffe, Ivy Barua, J. F. S. Batson, J. T. Bavington, J. R. Bell, M. S. Benett, R. B. Bennet, M. J. P. Berkley, L. S. Bernstein, F. A. Best, G. J. Biggam, Margaret A. Birchall, T. A. P. Birkett, H. E. Black, Paula D. Black, Margaret I. Blackhall, H. R. Blair, A. J. Blakeman, J. R. Blatch, A. I. Blenkinsop, R. Bolton, G. T. K. Boughey, C. J. Brigimen, J. M. Bristow, J. Brosnan, A. H. Brittain, H. C. I. Bywater, J. R. Burwell, G. L. Caley, I. Capperauld, C. J. Carr, J. V. F. Catto, A. J. McM. Cavenagh, E. C. Cawte, T. K. Cheah, J. P. Ah Fee Chui Wan Cheong, J. M. Clark, C. B. Clennar, Marjory Clowsley, J. H. Cochrane, M. D. Coulter, Izette R. Coulton, G. F. Counsell, G. Cowie, J. Coyer, T. A. Crantock, A. D. Crawford, Alison S. E. Crewdson, Katharine E. Cuthbert, P. G. Dale, S. Datta Chowdhury, D. Davies, Gwyneth M. Davies, H. T. Davies, L. M. Davis, J. A. Davis, Brigid C. C. Davison, H. Dawson, Lalita V. Deshpande, C. Diamond, W. R. Dick, B. C. Dixon-Warren, Phyllis E. D'Netto, K. E. Doran, G. S. Duncan, H. J. H. Dunn, D. Eakins, V. A. Economides, Elizabeth M. Edmunds, J. G. Elias, Elizabeth Elliott, P. J. Ellis, R. W. Elsdon-Dew, L. A. Emanuel, P. J. Enoch, C. D. G. Evans-Prosser, M. W. Everitt, D. R. Farmer, B. E. Farnham, L. J. Farrow, B. A. Fernando, N. Ferozuddin, H. W. Fladee, I. M. Fletcher, Janet A. Fletcher, K. Flintan, H. B. B. Forshaw, W. Fox-Russell, H. J. L. Francis, P. I. Frank, A. K. Fulton, N. H. N. Gardner, P. T. Gardner, R. Gardner, A. J. A. Garlant, T. H. Geddis, Jennifer M. R. Gilchrist, A. A. Gildersleve, P. G. Gillam, P. J. Gillies, R. T. Glen, J. E. Godrich, H. L. Goldwater, D. J. Goodman, I. S. Governor, C. B. T. Grant, Ellen C. G. Grant, J. N. S. Green, R. C. Grieve, Monica M. Gurnhill, S. Gurung, D. D. Guy, C. A. A. Haigh, K. C. Hammond, Margaret E. Hanlon, D. R. W. Hartley, D. C. Harvey, Beryl Heap, W. R. Heaton, R. Heslop, Anne S. Hill, D. M. C. Hislop, E. J. Horgan, J. L. Horner, G. R. Horton, Janet M. Houlston, Judith C. Howard, Mary S. Howell, K. K. Htway, H. I. Humphreys, G. B. Hunt, Florence S. Iswariah, Irene M. J. Jackson, T. Jenkins, H. C. Jennings, H. H. John, Saramma John, A. D. S. Johnson, R. W. Jones, V. D. Jones, Mary O. Joseph, H. O. Karoum, Audrey King, H. J. Kosasky, S. Krzaniak, I. McA. Kyles, H. O. Latham, A. B. Lavelle, A. R. Leader, Eva H. Letchner, L. Lewis, T. Lind, Rhona Lindup, H. K. Litherland, Nesta E. Lloyd, J. A. London, C. Lucey, Grania McCarthy, S. F. McCarthy, D. R. McCoy, J. S. McCracken, K. H. McCraith, A. H. Macdonald, B. M. McGibbon, R. D. Macgill, D. B. MacGregor, D. McLeman, June M. McLeod, I. S. Macmillan, A. D. McNeill, J. M. Maguire, Frances S. F. Mao, J. Martin, J. Mason, B. S. Mather, G. Mathew, M. T. May, M. A. Melsom, P. H. Merry, J. C. Merrington, J. Miller, Margaret K. Miller, Patricia A. R. Miller, A. R. Milne, C. A. Milner, B. A. E. Mindham, Zakia Minhas, A. V. Mitchell, Katherine M. Moore, D. J. Moorhouse, H. M. Moorhouse, D. H. Morgan, A. B. Morphy, J. L. Morrison, B. Mukherjee, J. P. Mumford, D. F. Munro, M. Murchison, K. V. Narumalani, Marjorie S. Newton, W. P. L. O'Driscoll, S. S. I. Parker, H. V. Parry, Mary W. Parry, A. G. P. Paton, P. W. S. Patton, G. W. Peacock, J. L. Penny, J. H. Perry, Mary Philipose, R. M. Phillips, R. Pilkington, A. J. Pim, Sylvia J. Pinder, H. D. W. Plowright, Mary S. Plumbly, D. Powell, C. J. Primmer, D. J. H. Prosser, R. L. Pyle, J. D. Raiman, C. Rao, M. J. Raphael, L. R. Redman, Marguerita Regan, Elizabeth M. Riddell, C. J. Roberts, K. K. T. Robertson, K. D. Robinson, F. D. Roche Kelly, L. C. Rose, D. F. Rowlands, S. Roy, I. B. Roy Chowdhury, D. G. L. K. Russell, I. A. Ruthven-Stuart, M. E. R. Samson, Algine M. Sansoni, Harendra N. Sarmah, J. MacD. Scott, R. S. C. Scoular, A. M. Segal, C. A. Selway, R. A. Sharpe, M. C. Sharrard, M. G. Shelton, K. I. Shimmings, Joyce K. Siromoni, B. A. M. Smith, R. N. Smith, S. Sorkin, F. M. Spence, P. D. Sprackling, J. A. Stainton-Ellis, J. T. Stewart, K. K. Swe, E. Taylor, J. G. Thomas, Anne E. Treharne, M. E. Tuck, J. L. Tuton, J. C. Twomey, V. R. Twyman, I. H. M. Veitch, J. Viner, U. Viswalingam, R. O. Walker, Sheila J. Wallace, M. T. Ward, A. F. Watson, Nancy M. Watts, J. L. Webster, J. Weston, B. R. Wheeler, D. M. Whiteford, Nora E. Wild, R. E. Wild, M. C. T. Wilkes, R. K. Wrennall, A. F. Wright, O. H. Yeo, Carmen K. M. Yuen.

Vital Statistics

Health of Scotland

The infant mortality rate in Scotland in 1959 was 28.4 per thousand live births. This was a little higher than in 1958, and high in comparison with some other countries. The rates in Glasgow and other industrial areas help to contribute to this state of affairs, since the rate for Glasgow in 1959 was 35.3.

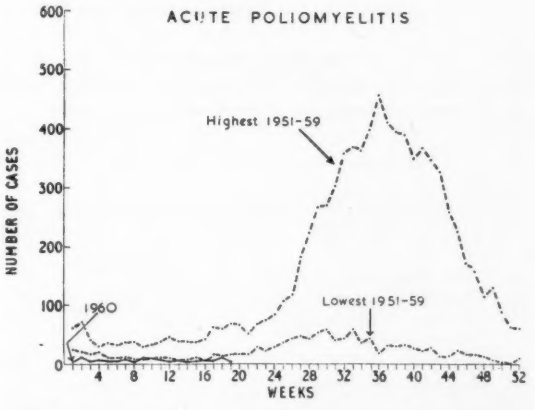
Among adolescents and young adults the general mortality rate in 1959 was low, but about 34% of the deaths in this age group (15–24) were caused by accidents.

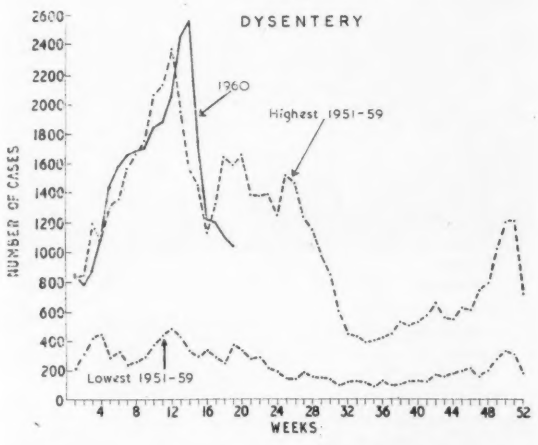
The notifications of dysentery in Scotland in 1959, at 10,186, were about 14% above the figures for the previous year. Glasgow and Dundee had a relatively high incidence.

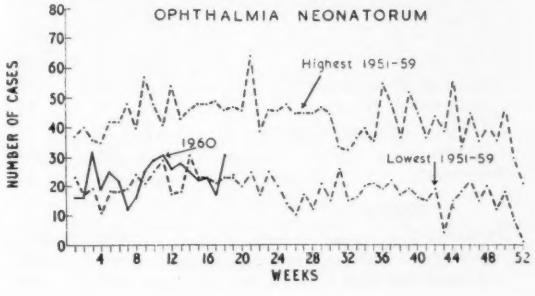
The demand for hospital treatment for patients suffering from pulmonary tuberculosis has continued to fall, as has the average duration of stay (from 154 days in 1954 to 80 days in 1959). The number of hospital beds in Scotland occupied by patients suffering from tuberculosis at the end of 1959 was 2,223, compared with 5,149 at the end of 1955. Nearly 1,000 beds used for the treatment of the tuberculous became redundant, and about half of these were allotted to the chronic sick.—*Report of the Department of Health for Scotland, 1959*, 1960, H.M.S.O., Edinburgh.

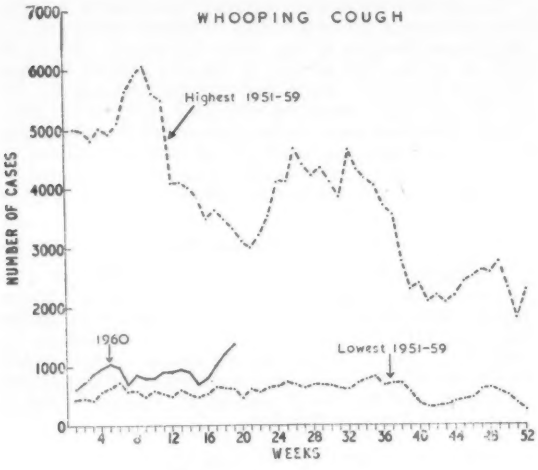
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

Dysentery	Week Ending May 7	Week Ending May 14
Cheshire	48	**42**
Wallasey C.B.	12	**13**
Alderley Edge U.D.	3	**11**
Essex	68	**73**
West Ham C.B.	9	**20**
Chigwell U.D.	12	**10**
Romford M.B.	9	**12**
Dunmow R.D.	0	**11**
Hampshire	23	**26**
Bournemouth C.B.	9	**10**
Lancashire	196	**213**
Liverpool C.B.	30	**35**
Oldham C.B.	13	**13**
Accrington M.B.	3	**13**
Morecambe and Heysham M.B.	21	**15**
Urmston U.D.	11	**20**
Worsley U.D.	16	**18**
London	144	**129**
Hackney	14	**14**
Islington	19	**26**
Southwark	12	**12**
Wandsworth	16	**15**
Norfolk	50	**64**
Norwich C.B.	34	**41**
Nottinghamshire	24	**31**
Nottingham C.B.	6	**13**
Sussex	13	**17**
Horsham R.D.	0	**12**
Warwickshire	16	**20**
Birmingham C.B.	11	**14**
Yorkshire West Riding	106	**81**
Bradford C.B.	24	**23**
Leeds C.B.	13	**22**
Sheffield C.B.	16	**10**
Glamorganshire	27	**35**
Bridgend U.D.	0	**10**
Ogmore and Garw U.D.	16	**13**
Glasgow	126	**126**
Edinburgh	28	**22**
Measles		
Lancashire	446	**649**
Liverpool C.B.	123	**159**
Manchester C.B.	63	**80**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 7** (No. 18) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	2	1	0	0		3	0	2	0	2
Dysentery	1,096	144	323	11	14	1,035	106	234	16	4
Encephalitis, acute	0	0	0	0		0	0		0	
Enteric fever:										
Typhoid	1	0		1		7	0	1	0	
Paratyphoid	4	0		0		10	1	1 (B)	0	
Food-poisoning	121	22	27	2		285	72	8	4	
Infective enteritis or diarrhoea under 2 years				7	15				5	13
Measles*	1,575	106	52	9	26	15,726	638	491	455	264
Meningococcal infection	14	3	8	1	1	19	0	6	1	2
Ophthalmia neonatorum	31	2	4	0		32	1	4	0	
Pneumonia†	292	21	202	1	6	303	13	159	10	3
Poliomyelitis, acute:										
Paralytic	7	1	0	1	3	5	1	0	1	
Non-paralytic	3	1	1			8	1	2		
Puerperal fever§	143	25	8	3		197	32	15	0	
Scarlet fever	533	30	57	23	13	1,016	61	72	33	20
Tuberculosis:										
Respiratory	416	67	49	18		539	63	84	16	
Non-respiratory	56	4	7	2		77	7	16	0	
Whooping-cough	1,201	87	282	8	46	647	31	93	44	101

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	0	0	0	0	0	0	0	0		0
Dysentery	4	0		0		4	0			
Encephalitis, acute		0			0		1			0
Enteric fever	0	0	0	0		1	0	0		
Infective enteritis or diarrhoea under 2 years	10	1	0	1	0	6	0	1		3
Influenza	22	1	2	0	1	21	0	0		3
Measles		0	0	0	0		0	1		0
Meningococcal infection		0	0				0	1		
Pneumonia	596	41	24	20	7	450	32	20		6
Poliomyelitis, acute	0	0		0	1	0	0			0
Scarlet fever		0	0	0	0		0	0		0
Tuberculosis:										
Respiratory	71	5	6	0	3	80	9	3		0
Non-respiratory		3	0	0	0		2	0		0
Whooping-cough	2	1	0	0	0	1	0	0		1
Deaths 0–1 year	288	18	21	9	17	300	34	29		30
Deaths (excluding stillbirths)	10,186	784	574		163	9,454	756	569		174
LIVE BIRTHS	15,475	1271	1083	317	461	14,967	1253	1059		445
STILLBIRTHS	328	31	19			324	30	16		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Chair of Morbid Anatomy, London University

Dr. ISRAEL DONIACH, reader in morbid anatomy at the Postgraduate Medical School of London, has been appointed to the university chair in that subject at the London Hospital Medical College.

Dr. Doniach, who was born in London in 1911, qualified M.B., B.S. from University College Hospital, London, in 1934, and took his M.D. in pathology in 1936. He became assistant in morbid anatomy at St. Mary's Hospital in 1935, and went from there in 1937 to Mount Vernon Hospital as clinical pathologist and research assistant. In 1943 he joined the pathology department of the Postgraduate Medical School as senior lecturer, and has held his present post there since October, 1959. His publications have included work on the lungs in uraemia, renal complications of pregnancy, the histology of gastric and intestinal biopsies, and studies of siderocytes. His earlier work in experimental pathology was concerned mostly with the photodynamic activity of carcinogenic hydrocarbons and more recently with the carcinogenic potentialities of radioactive iodine on the thyroid. He has also studied experimental physiological aspects of thyroxine synthesis, the action of antithyroid drugs, and thyroid regeneration.

Chair of Administrative Medicine, Glasgow

Dr. C. H. FLEMING has been appointed to the recently established chair of administrative medicine at Glasgow University.

Dr. Fleming has been dean of the faculty of medicine in the university since his appointment as reader in administrative medicine early last year. He took his M.D. at Glasgow in 1933 and joined the Department of Health for Scotland in 1937, becoming a principal medical officer in 1946. He became F.R.C.P.Ed. in 1952.

British Paediatric Association

The officers appointed for 1960 to 1961 are: *President:* Professor A. V. NEALE; *President-Elect:* Professor A. A. MONCRIEF; *Treasurer:* Professor A. G. WATKINS; *Secretary:* Dr. E. W. HART (c/o Institute of Child Health. The Hospital for Sick Children. Great Ormond Street, W.C.1).

Faculty of Ophthalmologists

The following have been elected officers for 1960 to 1961: *President:* Mr. E. G. MACKIE; *Vice-Presidents:* Mr. J. E. M. AYOUB, Mr. GEORGE W. BLACK; *Honorary Treasurer:* Mr. G. T. WILLOUGHBY CASHELL; *Honorary Secretary:* Mr. J. R. HUDSON.

Medical Sickness, Annuity and Life Assurance Society

At the 75th annual general meeting of the Medical Sickness, Annuity and Life Assurance Society, founded in 1884 for doctors by doctors, Mr. R. J. MCNEILL LOVE, the chairman, reported "a record figure of new business" for 1959.

For the first time the annual increase in membership exceeded 1,000, bringing the total to 19,462. During 1959 the requirements for medical examinations were modified, and a further scheme has since been introduced under which a proposal for sickness benefit may be considered without the need for any medical examination. The total premium income of the Funds now exceeds £1m. The Sickness Insurance Fund stands at over £3¼m., and the Life Assurance and Annuity Fund at £5¾m., the latter having increased by over £400,000 during the year. A substantial part of the profits realized from the sale of investments has been used to increase the Reserve Fund from £350,000 to £500,000.

Medical Widows and Orphans

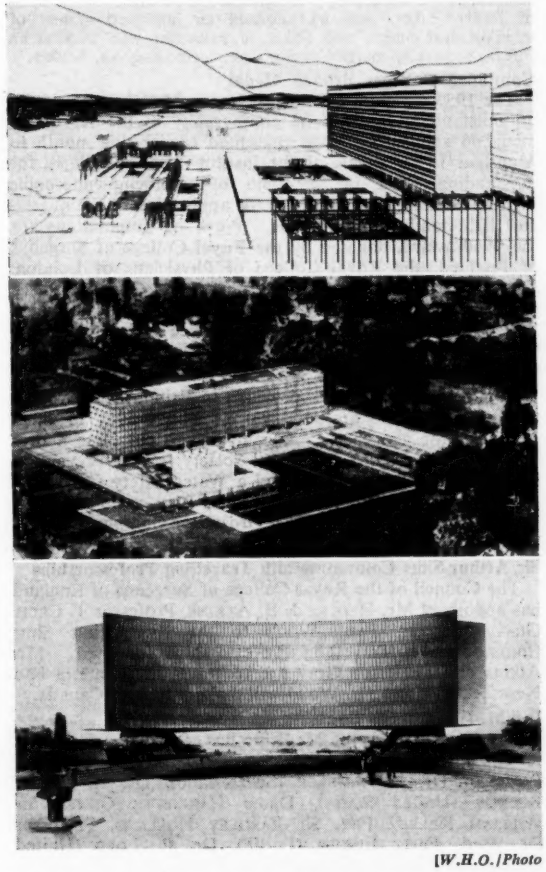
Dr. W. E. LLOYD was elected president of the Society for Relief of Widows and Orphans of Medical Men at the annual meeting on May 18, in succession to the late Sir ROBERT YOUNG. Sir ERNEST ROCK CARLING and Dr. J. A. STRUTHERS remain treasurer and secretary respectively. It was reported at the meeting that one widow who died last year had been in receipt of benefits from the Society for 46 years. Membership is open to male registered medical practitioners who at the time of election are resident within a 20-mile radius of Charing Cross. Further details may be obtained from the secretary at 11, Chandos Street, Cavendish Square, London, W.1.

Merck Sharp and Dohme Fellowship

To mark the opening of their new drug factory last week, the pharmaceutical firm of Merck Sharp and Dohme Ltd. have founded a fellowship of £7,500 for research into metabolic diseases. The Dean of Westminster Medical School (Dr. RICHARD BAYLISS) will be chairman of a small committee to administer the project and choose a Fellow. At a luncheon on the same occasion the managing director, Mr. T. W. RAYNER, reviewed some of the achievements of his firm and the drug industry. Unlike the farming, steel, and aircraft industries, he said, they received no help from the Government. There had recently been much criticism of the profits made in the pharmaceutical industry. It had been said that it was subsidized by the N.H.S.—"The truth is that the pharmaceutical industry is subsidizing the National Health Service."

W.H.O. Headquarters Architectural Competition

The international architectural competition for the design of a new headquarters building for the World Health Organization has been won by Professor JEAN TSCHUMI, of the Polytechnical School, Lausanne (centre). The second prize goes to EERO SAARINEN, America (bottom), and the third to J. DUBUISSON, of France (top).



[W.H.O. Photo

The winner's design is for a 10-story building covering 16,425 square metres. It has a "curtain" façade of glass walls with aluminium sun-break elements on a framework of reinforced concrete covered with marble. Situated near the Palais des Nations, it will take three years to build, beginning next year.

Defoe's Tercentenary

The tercentenary of Daniel Defoe, who among his other claims to fame published in 1698 details of a contributory health and pensions scheme, is being marked by an exhibition at Stoke Newington, where he lived for a large part of his life.

Defoe's *An Essay upon Projects* proposes the establishment of a pensions office that for sixpence down and a shilling a quarter should appoint physicians and surgeons for its members, should either cure the disabled or allow them a pension—sailors, who ply a dangerous trade, are considered separately—and should provide hospitals for the aged infirm. His elaborate financial calculations allow £100 a year each for a physician and surgeon, and are worked out on the basis of a death-rate of one in 40 a year. To safeguard mental defectives Defoe proposed the erection of "a fool-house for all that are born fools" and suggests that it should be maintained by a tax on learning to be paid for by the authors of books. Those who mocked the insane should help to pay for their upkeep by being fined. He wanted an academy for the purification of the English language, but excluded doctors because of "the habits of speech peculiar to their practice." He took a great interest in the work of Henry Baker, who had devised an improved system of teaching deaf mutes, and Baker, a naturalist who became an F.R.S., eventually married Defoe's youngest daughter, Sophia.

Combined Colleges Bronze Medal

The 1959 Combined Colleges Bronze Medal, awarded for an outstanding example of photography in the service of medicine and surgery, was presented earlier this month to Monsieur J. VULMIÈRE, of the Institut d'Optique, Paris, for outstanding work in the field of photociné-endoscopic instrumentation, particularly in the application of the quartz-rod light-conducting principle. Work or nominations for the 1960 award, donated by the Royal College of Surgeons of England, the Royal College of Physicians of London, and the Royal College of Obstetricians and Gynaecologists, should reach the honorary secretary of the Medical Group, Royal Photographic Society, 16, Prince's Gate, London, S.W.7, by September 30.

Water Safety Code

About 1,000 people are drowned in Britain every year—the majority while on holiday—and about 30% of them are under the age of 15. A campaign to cut these figures has been launched by the Royal Society for the Prevention of Accidents, which has devised a Water Safety Code containing do's and don'ts for all who play, swim, or sail. It costs 6d. from the society, 52, Grosvenor Gardens, London, S.W.1.

Sir Arthur Sims Commonwealth Travelling Professorships

The Council of the Royal College of Surgeons of England has appointed Mr. HEDLEY J. B. ATKINS, Professor T. CECIL GRAY, and Dr. PAUL WOOD to the Sir Arthur Sims Commonwealth Travelling Professorships for 1961. Mr. Atkins and Professor Gray are to travel in Australia and New Zealand, and Dr. Wood will make a tour of Canada.

R.S.M. Honorary Fellows

The Royal Society of Medicine has elected the following to honorary Fellowship: Dr. F. E. ADAIR (United States), Professor Dr. M. AMSLER (Switzerland), Dr. H. LEROY BOCKUS (United States), Dame HARRIETTE CHICK, Sir WILLIAM KELSEY FRY, Sir EARDLEY HOLLAND, Professor Dr. Med. FRITZ LINDER (Berlin), Dr. R. LOEB (United States), Sir PHILIP MANSON-BAHR, Professor J. H. MEANS (United States), Sir CLEMENT PRICE THOMAS.

In Brief . . .

The National Physical Laboratory's ACE computer has been started on a five-year programme of translating Russian papers on mathematics and electronics into acceptable English.

The Swedish State Tobacco Monopoly is offering a free heart and lung examination to inhabitants of Stockholm and Gothenburg who smoke more than 20 cigarettes a day. The tobacconists supply the application forms.

People in the News

Professor IAN AIRD is in Athens to advise on the School of Postgraduate Medicine which is planned for the Evangelismos Hospital there. He will later be a guest at the Middle East Conference of Surgeons.

Dr. W. A. CONNOLLY, first president of the Australian College of General Practitioners, is visiting Britain and will represent the New South Wales Branch at the Annual Representative Meeting of the B.M.A. at Torquay next month.

Professor B. A. HOUSSAY, director of the Institute of Biology and Experimental Medicine, Buenos Aires, will be among those given the degree of D.Sc. *honoris causa* of Cambridge University in July.

Dr. DAVIDSON NICOL, senior pathologist to the Sierra Leone Government, has been appointed principal of Fourah Bay College, the University College of Sierra Leone.

COMING EVENTS

Worshipful Society of Apothecaries of London, Faculty of History of Medicine and Pharmacy.—First Annual Students' Lecture: "William Harvey: Pioneer of Medical Science," by Dr. K. D. KEELE, Apothecaries' Hall, June 2, 5.30 p.m., followed by colour-film on Harvey's life and work and conducted tour of Hall. Admission by ticket only, from deans of medical schools.

British Psycho-Analytical Society: Ernest Jones Lecture.—Professor STUART HAMPSHIRE: "Disposition and Memory," June 15, 8.30 p.m., Barnes Hall, Royal Society of Medicine.

International Society of Geographical Pathology.—7th International Conference, "Eclampsia and Pre-eclampsia in Pregnancy," Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, June 28–30. Details from Professor J. S. YOUNG, Department of Pathology, Aberdeen University, Foresterhill, Aberdeen.

Medical Society for Study of Venereal Diseases.—Liverpool meeting, July 8 and 9. Details from the Honorary Secretary of the Society, Dr. N. MASCALL, 39, Devonshire Place, London, W.1.

R.C.S.(Edin.) and Edinburgh Postgraduate Board.—Revision course: "Operative Surgery and Surgical Pathology," beginning July 11. Details on advertisement p. 62.

3rd International Medical Electronics Conference.—Olympia, London, July 21–27. It is hoped that the subjects discussed will include instrumentation for medicine and biology; medical electronics in space research; isotopes and radiology; ultrasonics and microwave radiation; the respiratory system, digestive system, metabolism and biochemistry; the circulatory system; electronic aspects of sight, hearing, and locomotion; the motor and nervous systems. Details from the Secretary, Institution of Electrical Engineers, Savoy Place, London, W.C.2.

Davidson Clinic for Analytical Psychotherapy.—Summer school: "The Contribution of the Psychological Clinic to the Community," July 27–August 2. Details from the secretary of the clinic, 58, Dalkeith Road, Edinburgh, 9.

2nd U.N. Congress on Prevention of Crime and Treatment of Offenders.—Church House and Carlton House, London. August 8 to 20. Details from the secretariat of the Congress, Horseferry House, Dean Ryle Street, Westminster, London, S.W.1.

11th International Astronautical Congress.—Stockholm, Sweden, August 15–20. Details from the Congress Secretariat, Box 5045, Stockholm, 5, Sweden.

1st International Congress of Histochemistry and Cytochemistry.—Paris, August 28–September 3. Details from Dr. R. WEGMANN, Institut d'Histochimie Médicale, 45, rue des Saints-Pères, Paris, 6, France.

NEW ISSUES

BRITISH JOURNAL OF VENEREAL DISEASES

Editorial.
I.U.V.D.T. Report of the Secretary-General.
I.U.V.D.T. and W.H.O. T. Guthe.
Programme Opportunities for I.U.V.D.T. N. Acton.
Recent Achievements of a Non-governmental Organization in V.D. Control. E. G. Clark and C. van Hyning.
Present Status of the Management of Cardiovascular Syphilis. B. Webster.
An Account of the So-called Reiter Treponeme. H. Reiter.
Systemic Treatment of Trichomoniasis with a Derivative of Nitro-imidazole, 8823 R.P. P. Durel, V. Roiron, A. Siboulet, and L. J. Borel.
Uveitis, Arthritis, and Non-specific Genital Infection. R. D. Catterall.
An Evaluation of the Incidence of Reactions to Penicillin. W. J. Brown.
Penicillin Resistance in Gonorrhoea. A. J. King.
Surface Manifestations of Reiter's Disease in the Male. J. A. H. Hancock.
Incidence of Treponemal Diseases in a Group of Immigrants in East London. E. M. C. Dunlop.
Social Status and Sex Habits of Immigrants attending a V.D. Clinic in London. C. S. Nicol, G. S. Bird, M. Brinton, and M. S. Rigden.
Migration as a Factor in V.D. Programmes in the U.S.A. W. J. Brown.
Obituary.
Abstracts.

Volume 36, No. 1. (Quarterly; £3 annually.)

ANNALS OF THE RHEUMATIC DISEASES

Heberden Oration. The Proteins of Connective Tissue and Their Metabolism. A. Neuberger.
The Lubrication of Animal Joints in Relation to Surgical Reconstruction by Arthroplasty. John Charnley.
Benign Polyarthritis. J. S. Lawrence and P. H. Bennett.
Chondrocyte Function of Human Articular and Costal Cartilage Compared by Measuring the In Vitro Uptake of Labelled (^{35}S) Sulphate. T. F. McElligott and D. H. Collins.
Use and Interpretation of the Antistreptolysin Test. H. S. Lawy.
Production of Lupus Erythematosus (L.E.) Cells in the Dog by the Transfusion of Systemic Lupus Erythematosus Plasma. George Bencze with Mary Ludányi.
2,4,6-Trihydroxybenzoic Acid in the Treatment of Rheumatic Fever. E. B. D. Hamilton and E. G. L. Bywaters.
Erythrocyte Survival in Rheumatoid Arthritis. S. M. Lewis and I. H. Porter.
Book Reviews.
X International Congress of Rheumatology, 1961.
Heberden Society. Annual Report, 1959.
New Zealand Rheumatism Association. Annual Report, 1959.
Brazil.
VI International Congress of Internal Medicine, 1960.
Abstracts.

Volume 19, No. 1. (Quarterly, £3 annually.)

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, May 28

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Lecture Room "B," Addenbrooke's Hospital, Cambridge, Symposium on General Medicine by the Medical Registrars. Morning: 10.30 a.m., Dr. D. W. Barkham: Problem of Pulmonary Embolism; 11.30 a.m., Dr. M. J. Purves: Aetiology and Investigation of Pleural Effusions; 12.15 p.m., Dr. R. Hill: Hypoglycaemic Drugs in Diabetes Mellitus. Afternoon: 2.30 p.m., Demonstration and Discussion of Clinical Cases; 3.45 p.m., Dr. H. Eckert: Treatment of Thyrotoxicosis.

Monday, May 30

LONDON UNIVERSITY.—At University College Hospital Medical School, 5 p.m., special university lecture in medicine by Professor M. K. Krishna Menon (Madras): Evolution of the Curative Treatment of Eclampsia.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor John Crofton: Problem of Tuberculosis.
UNIVERSITY COLLEGE LONDON.—At Chemistry Theatre, Gower Street, W.C., 5.30 p.m., Hobhouse Memorial Lecture, 1960, by Sir Aubrey Lewis: Agents of Cultural Advance.

Tuesday May 31

CAMBRIDGE UNIVERSITY POSTGRADUATE MEDICAL SCHOOL.—At Radiotherapeutic Centre, Addenbrooke's Hospital, 4 for 4.15 p.m., Dr. G. F. Watson (Kitchener, Ontario): Treatment of Cancer Cases with Spleen Extract Given Intravenously and a Concentrated Extract Given Subcutaneously.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. E. Bodkin: Applied Physics II.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 3 p.m., Mr. W. Hawksworth: Vaginal Hysterectomy.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Dr. Mavis Gunther: Physiology and Management of Human Lactation.
WILLIAM TEMPLE ASSOCIATION.—At 24, South Audley Street, London, W., 8 p.m., Reverend G. R. Dunstan: Suicide.

Wednesday, June 1

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. V. H. Witten: Use of Ionizing Radiation in Dermatology.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. R. V. Gibson: Open lecture on Atrial and Ventricular Septal Defects.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 3 p.m., Professor N. C. Louros (Athens): Fallacies of Our Recording System Concerning Carcinoma of the Cervix.
MANCHESTER MEDICAL SOCIETY: SECTION OF GENERAL PRACTICE.—At Withington Hospital, Manchester, 4 p.m., clinical meeting.
OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Professor G. L. Montgomery: Some Observations on the Pathology of the Myocardium.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. D. W. Henderson: Experiments on Primary and Secondary Respiratory Infection.
ROYAL INSTITUTION.—9 p.m., Professor G. C. Drew, M.A.: Alcohol and Skilled Performance.

Thursday, June 2

HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Professor M. F. A. Woodruff: New Approaches to the Treatment of Cancer.
LONDON UNIVERSITY.—At Guy's Hospital Medical School, 5.30 p.m., university lecture in biochemistry by Professor C. Liebecq (Liége): Biochemical Aspects of Glucose Utilization in Muscle Tissue.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. M. French: Adult Coeliac Disease and Allied Disorders.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., postgraduate demonstration by Dr. M. Partridge: Psychiatry.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. S. J. Bach: Metabolic Fate of Protein-Nitrogen in the Mammal—(2) Biosynthesis of Urea.

Friday, June 3

ABERDEEN UNIVERSITY: DEPARTMENT OF SURGERY.—At Medical School, Foresterhill, 5 p.m., Mr. J. H. Johnston: Burns.
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. M. Feiwel: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. L. Livingstone: clinical demonstration.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. Denis Browne: Spina Bifida.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Dr. Cedric Carter: Mongolism and other Conditions due to an Abnormal Number of Chromosomes.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—J. K. Chaudhry, M.B., B.S., Surgical Registrar, Ipswich and East Suffolk Hospital; B. A. Athley, M.B., B.S., Surgical Registrar (Casualty), Peterborough Memorial Hospital; A. J. Mackintosh, M.B., Ch.B., Registrar in Obstetrics and Gynaecology, West Norfolk and King's Lynn General Hospital; J. R. M. Davidson, M.B., Ch.B., F.R.C.S.Ed., Surgical Registrar, Norfolk and Norwich Hospital.
HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—Ruth F. Harris, M.B., B.S., D.C.H., and Ritsa Papatheophilou, M.D., Senior Registrars to Department of Clinical Neurophysiology.
LEIPER, JOHN, M.B.E., M.B., Ch.B., D.P.H., County Medical Officer, Cumberland
LIVERPOOL REGIONAL HOSPITAL BOARD.—J. Browne, M.D., D.P.M., Whole-time Consultant Psychiatrist and Deputy Medical Superintendent, Deva Hospital, Chester; Millicent M. Rogerson, M.B., B.S., D.C.H., Whole-time Senior Resident Medical Officer (S.H.M.O.), Olive Mount Children's Hospital, Liverpool; D. F. MacCarthy, M.B., B.Ch., Whole-time Senior Casualty Officer to Chester and District Hospital Management Committee; N. Coulshed, M.D., M.R.C.P., Whole-time Consultant Physician in Cardiology to Regional Cardiac Centre based at Sefton General Hospital; Eileen P. Scanlan, M.B., B.Ch., D.P.M., D.Obst.R.C.O.G., and E. E. Clarke, M.D., M.R.C.P.I., D.P.M., Whole-time Assistant Psychiatrists at Rainhill Hospital; K. H. Slatter, M.D., M.R.C.P., Part-time Consultant Neurologist, and P. H. Buxton, M.D., M.R.C.P., Whole-time Consultant Pathologist, to Regional Neurosurgical Unit at Walton Hospital.
YARROW, ALFRED, M.B., Ch.B., D.P.H., Area Medical Officer and Divisional School Medical Officer for Essex County Council and Medical Officer of Health to Benfleet, Canvey Island, and Rayleigh Urban Districts and Rochford Rural District Councils.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Breese.—On May 18, 1960, at Holbeach Hospital, Spalding, Lincs, to Anne, wife of James Breese, a third son—William Richard.

MARRIAGES

Catchpool.—On May 14, 1960, at Beverly Hills, California, U.S.A., J. Frank Catchpool, M.B., B.S., M.R.C.S., L.R.C.P., to Adriana Calles Eller.

DEATHS

Bonner.—On May 12, 1960, at St. John's Wood, London, N.W., William Percy Bonner, M.R.C.S., L.R.C.P., late of Peterborough.
Denz.—On May 14, 1960, at Dunedin, New Zealand, Frank Anton Denz, M.D., formerly of Wallington, Surrey.
Friedlander.—On May 13, 1960, at Auckland, New Zealand, Hugo Rudolph Friedlander, M.R.C.S., L.R.C.P.
Hopkins.—On May 11, 1960, at 79, Bryanston Court, London, W., Lady Lucy Hopkins, M.B.E., M.B., Ch.B., D.P.H.
Joynt.—On May 10, 1960, at Royal Naval Hospital, Plymouth, Devon, Christopher Noble Holton Joynt, M.B., Ch.B., Surgeon Captain, R.N., retired.
Lawrie.—On May 14, 1960, at 41, Brecon Road, Handsworth, Birmingham, Warwicks, Hugh Lawrie, M.B., C.M., D.P.H., late of Ramsbottom, Lancs.
Long.—On May 1, 1960, William Christopher Long, M.R.C.S., L.R.C.P., D.M.R.E., Major, I.M.S., retired, of Greystones, Tunbridge Wells, Kent.
MacPherson.—On May 7, 1960, at Royal Infirmary, Edinburgh, Alexander Douglas Haig MacPherson, M.D., of Hillcrest, Kennoway, Fife.
Saward.—On May 5, 1960, at Summers Ardingly, Sussex, Arthur Henry Michael Saward.
Warwick.—On May 10, 1960, at Paignton, Devon, Frank Phillips Warwick, D.S.O., M.B., Ch.B., Lieutenant-Colonel, I.M.S., retired, aged 79.
Wilson.—On May 9, 1960, David Cook Wilson, V.R.D., M.D., F.R.C.P.Ed., of 13, Ardross Street, Inverness.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Birth Risks in Haemophilic Babies

Q.—*The wife of a haemophiliac is pregnant. Is there any risk of haemorrhagic incidents in the baby at birth if it is a boy and has inherited the haemophilia from its father?*

A.—In the unlikely event of the wife being a carrier and the husband suffering from haemophilia, it is theoretically possible not only for the male but even female offspring to be haemophiliacs. But haemophilia of the classical type—i.e., that due to a lack of anti-haemophilic globulin—is not transmitted as a manifest disease by the male. It is transmitted by female "carriers." The adverse gene is linked with an X sex chromosome, but the presence of a normal allelomorphic gene on the second X sex chromosome in the female prevents the appearance of the disease in this sex. No such gene is found on the Y sex chromosome and the disease is therefore ordinarily manifested only by the male. It follows that unless the wife in this case comes from an affected family and is herself a carrier, none of the children will suffer from overt disease, and none of the males will be tainted in any way. All the females born of this union, however, will, by virtue of an abnormal gene on the X chromosome inherited from the father, prove to be carriers.

It may be added that any baby born suffering from haemophilia is only liable to haemorrhage if it sustains trauma during or after birth. A break in tissue continuity at any site under such circumstances would be more likely to bleed excessively.

Antithyroid Drugs and Cretinism

Q.—*A 28-year-old woman has a 4-year-old child. During the past year she has developed thyrotoxicosis, which is responding very well to potassium perchlorate. She wants to have another child. What would be the risk of cretinism in the foetus?*

A.—There is no risk of inducing permanent cretinism in the foetus of a pregnant woman who is being treated with antithyroid drugs. A goitre may be present in the infant, but this seldom requires treatment. If the goitre is accompanied by evidence of hypothyroidism (of which the absence of the lower femoral epiphysis is the best objective sign), then L-thyroxine (0.01 mg. twice daily) may be used in treatment until the goitre disappears. Very rarely thyrotoxicosis has been reported in the infant of a thyrotoxic mother.[1] The cause of this is unknown.

If the maintenance dose of potassium perchlorate is reduced by one-half during the last month of pregnancy, then there should be no interference with the development of normal thyroid function in the baby. I am not aware of any report of a goitre having been discovered in the child of a mother in whom this prophylactic measure has been adopted.

REFERENCE

1 Lewis, I. C., and MacGregor, A. G., *Lancet*, 1957, 1, 14.

Response to Oxytocin

Q.—*Is it possible for a subject to be unduly sensitive to oxytocin so that a minimal dose could produce a most violent and precipitate labour?*

A.—The response to oxytocin varies widely from one uterus to another, and also, depending on other hormone influences, from time to time in the same uterus. Because its effect is unpredictable, oxytocin should not be given intramuscularly in divided doses until after the baby is born. An injection of even 1 or 2 units can have an alarming action on the uterus at term or in labour. The only safe method of inducing labour, or of treating inertia in early labour, is to give the oxytocin by continuous intravenous drip infusion of a solution made up of 2 units in 1,000 ml. of 5% glucose in water or saline. The rate of drip should initially be no more than 8–16 drips per minute, and should thereafter be modified according to the uterine response. If the uterus proves over-sensitive the effect of oxytocin disappears within approximately 5 minutes of discontinuing the infusion.

Cooking the Bacon

Q.—*What is the minimum degree and duration of temperature to which pork, bacon, sausages, etc., should be subjected to ensure that they are safe from hydatid and other infestations?*

A.—This question wrongly implies that pork, bacon, sausages, etc., are a source of human infection with hydatids. This occurs only when the eggs of *Echinococcus granulosus* are accidentally swallowed after being passed in the faeces of dogs, foxes, etc., which harbour this small tapeworm in the intestine. Pork and pork products are a source of human infection with *Taenia solium* and *Trichinella spiralis* (trichinosis). Meat containing the bladder-worm of *T. solium* (*Cysticercus cellulosae*) or cysts of *T. spiralis* should be subjected to a minimum temperature of 100° C. for half an hour for each kilogram of meat or equivalent.

Intravenous Iron

Q.—*In view of the doubt about the safety of giving iron dextran intramuscularly, can it be given intravenously? Alternatively, what is a suitable preparation to give in a case when iron cannot be given by mouth?*

A.—Iron dextran complex is not suitable for ordinary routine intravenous use. There are preparations containing saccharated iron oxide in sterile solution specially made for intravenous use which may be given with great safety and convenience. These preparations have been used very extensively with excellent clinical results.

Softening of the Cervix

Q.—*Does softening of the cervix occur otherwise than in pregnancy?*

A.—Softening of the cervix in pregnancy is due firstly to increased vascularity and later also to increased secretory dilatation of the cervical glands. Some softening of the cervix may occur otherwise than in pregnancy, and conversely the cervix in early pregnancy may fail to soften normally if scarred or fibrosed. Apart from pregnancy, any condition causing considerable local congestion might lead to softening of the cervix.

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